On the effect of sleep disturbance and affective disorders on patients on opiate replacement therapy

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Inhaltsverzeichnis

Abstract

Opiate addiction is a challenging and understudied area of medicine. There have been recent promising developments in the field of addiction medicine with the introduction of prolonged release buprenorphine depot buvidal; increasing number of diamorphine injection centres in Germany; and the widely available new oral antiviral therapy for hepatitis C. Recent studies indicate these have led to a decrease in mortality and improved quality of life for opiate-addicted patients. To further explore the potential positive effects, we conducted a cross-sectional study from 113 patients on opiate replacement therapy from two treatment facilities in Munich, Germany from September to November 2015. The study involved patients voluntarily completing questionnaires designed to document their somatic and psychiatric illnesses, drug abuse history and their current socio-economic status. The extent of their depression and sleep disturbances were measured by Becks Depression Inventory II and Pittsburgh Sleep Quality Assessment, respectively. Our primary aim was to identify the effects of opiate replacement therapies - methadone, levomethadone, buprenorphine and diamorphine - on patients with affective disorders and sleep disturbance. We also looked at the impact of benzodiazepine usage, chronic pain syndrome, and various social factors on opiate-addicted patients. Results from this study showed that patients treated with levomethadone suffered higher rate of depression and insomnia as compared to patients on other forms of opiate replacement therapies. Benzodiazepine usage had been commonly found in higher dosages in patients with affective disorders and its usage has been lowered comparably in the same group of patients with the appropriate usage of antidepressants. Benzodiazepines have also been used at higher dosages in patients suffering sleeping disturbances. Furthermore, patients who endured chronic pain tended to use higher doses of benzodiazepine and were more likely to be depressed. Being employed has also shown to be protective against insomnia. Overall, the patients in the study have confirmed a subjective improvement in the quality of their sleep since commencing opiate replacement therapy. The results from this cross-sectional study have provided us with an overview of the current health issues facing opiate addicts in these two opiate substitution practices in Munich and, in particular, assessing the burden of depression, insomnia and benzodiazepine abuse in conjunction with opiate replacement therapies. We hope that further studies will rise from the results of this study and help to improve future clinical practices.

Kapitel 1

Introduction

1.1 Opiate abuse

1.1.1 Epidemiology

Opiate addiction is a world-wide problem. Heroin was first introduced to the German drug market in the 1970's and since then there has been problematic increase in the number of users. Among these users, HIV infections and mortality rate also increased. This led to the implementation of harm reduction services such as syringe exchange centers, however, the first Methadone Maintenance Program or Opiate Replacement Therapy (ORT) was not started in Germany until 1987 in North Rhine Westphalia [1]. Methadone was initially only allowed to be given to patients who fulfilled strict criterion, such as pregnancy, extreme pain or life-threatening conditions of withdrawal. ORT can nowadays be prescribed in Germany by General Practitioners with additional training in Addiction Medicine. They have to complete admission documents detailing patient medical and illicit substance abuse history and examinations, as well as past treatments and planned treatment plans, collaborations with psychologists and social workers; as well as results of regular drug screening and blood results with HIV and Hepatitis Serology. Patients are also registered at the Federal Narcotics Board (Bundesopiumstelle) to prevent co-current substitution prescriptions from another doctor [1].

According to the data provided by the European Monitoring Center for Drug and Drug Addiction, it is estimated that in 2016 Germany had 150,943 high-risk opiate users between the ages of 15-64, with 77,200 heroin users currently in treatment. The mean age of first use is 22.6 years and the mean age of first entrance into maintenance treatment is 35.8 years. There has also been a 40-45% increase in the number of first-time opiate entrants into ORT between 2012- 2016 [2].

1.1.2 Opiate Replacement Therapy

Substance use disorders should be considered a chronic disease of the brain [3] and it has much in common with other chronic medical conditions, in that it has a multifactorial etio-

logy and requires both pharmacological and psychological interventions [4]. The ultimate goal of addiction treatment is to achieve abstinence from illicit drugs. Pharmacologic interventions of opiate addicted patients involve ORT and most addicts will remain on ORT to attenuate withdrawal symptoms, prevent relapse, reduce mortality and to normalize social dysfunction [5]. Permanent abstinence in this patient group is only around 10% [6]. The psychological therapy includes psychiatric, psychotherapeutic and social measures.

Benefits of ORT

ORT has been shown in Germany in 2006 to have decreased the mortality rate by 3 to 5 times compared to untreated heroin users; to reduce the concurrent usage of illicit drugs, leading to an improvement in the general health status of these patients [1]. It has shown to have a much higher patient retention rate compared to inpatient therapies, where there was a high dropout rate in the first 4 months and the patients would relapse immediately into opiate use [7]. A study comparing retention rates in ORT in different states in Germany in 1998 showed that Hamburg and Bremen had a retention rate of almost 80% after 2 years and 6 months [8].

Methadone

Methadone was developed in Germany between 1937-1939 [9] and was first introduced in the US in 1947 as an opiate analgesic, for its full agonist properties on the -opiate receptor [10]. However, its use as an ORT started in 1965 first at the Rockefeller University addiction Research Centre [5] and was first used in Germany in 1987. It is praised for being an orally effective medication with a longer half- life (24-36h) than heroin or morphine (1-5h) so it can be administered once daily [4, 11].

The initial dose of methadone shown to be safe even in opiate- native patients is between 20-40mg/day. The dose is slowly increased in the initial weeks every 5-7 days in accordance to individual tolerance and opiate withdrawal symptoms to an optimum dose. A stable plasma level is normally reached after 10 days [12].

Common side effects include vomiting, dizziness, fatigue, sexual dysfunction and poor sleep quality [13]. One of the known effects of methadone is QT prolongation and this has been associated with cardiac arrhythmias, in particular Torsade de Points. Thus, QT intervals should be assessed prior to commencing methadone therapy and closely monitored especially in patients with concurrent usage of certain groups of antipsychotic and antidepressants medications that also cause long QT syndrome, most notably the tricyclic antidepressant group. Methadone can also lead in higher doses, especially in combination with other agents such as, alcohol, opiates and sedatives, to sedation and respiratory depression [9].

Levomethadone

There are 2 forms of methadone available in Germany, those being levomethadone and racemic methadone, with the latter being approved for use in 1994. The rationale for

using racemic methadone is the direct treatment costs are around 20% lower than that of levomethadone. As of December 2003, there were 56,000 patients in maintenance treatment in Germany of whom 70% were treated with racemic methadone, 16% with levomethadone, 12% with buprenorphine and 1.6% with codeine. Racemic methadone and levomethadone can be replaced by each other on a 2:1 ratio [8].

Racemic methadone contains both R and S- enantiomers. The R- enantiomer is a receptor agonist responsible for therapeutic effects. The S- enantiomer only has a weak receptor agonist effect and can block hERG channels, which is a subunit of the potassium ion channel that mediates the cardiac polarising potential. This has been thought to be the cause of prolonged QT intervals in patients on methadone therapy [14]. Levomethadone contains only the R- enantiomer. It has a more potent opiate agonist and analgesic effect compared to racemic methadone and is thought to be safer in patients with pre-existing prolonged QT Syndrome. In addition, in a cross-sectional questionnaire-based telephone survey among physicians (n= 176) who provided outpatient ORT in Germany during 2015, patients on levomethadone have reported to have less fatigue, gastroenterological complaints and weight gain compared to patients taking racemic methadone [15].

Buprenorphine

Buprenorphine was first introduced in France in 1996 with approval in the following years in other countries as a treatment for opiate use disorders. Its usage as a substitution treatment in Germany by the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte) was approved in the early 2000's [1]. It is a long-acting partial opiate agonist with a slow dissociation from the -opiate receptor, which causes extended duration of action following single dose administration. The partial agonist activity also provides a better safety profile than the full - receptor agonists, causing reduced risk of overdose even when given at high intravenous doses, less euphoria and severity of withdrawal symptoms, even upon discontinuation [4, 16]. Buprenorphine can also produce a sufficient tolerance to block the effect of exogenously administered opiates, suggesting it might help with reducing opiate dependency [6]. Side effects are similar to those of methadone with the exception that it does not prolong QT interval. Patients have also reported to have a much clearer and conscious state of mind compared to being on methadone [1]. Buprenorphine has also been combined with naloxone under the trade name of Suboxone, an opiate antagonist at a 4:1 ratio in a sublingual form to prevent it from given intravenously. Patients do not experience the effect of withdrawal from naloxone after sublingual administration due to its low bioavailability [4] but will have an immediate opiate withdrawal syndrome if given intravenously. In Germany, Buprenorphine has been used frequently in pregnant patients resulted in considerably reduced or absent neonatal withdrawal symptoms. It can also be given every second day without significantly increasing withdrawal symptoms [16]. As of march 2019, buvidal, a weekly or monthly subcutaneous buprenorphine depot has been launched on the German market. It has been promised to provide effective suppression from cravings, allowing a higher quality of life by decreasing patient burden and stigma of opiate addiction [17]. The long-term clinical

effects and safety of buvidal are still waiting to be seen.

Diamorphine

Injectable diamorphine therapy as a form of ORT was introduced formally in Germany in 2009. As of 2013, there were 9 outpatient clinics in Germany across 7 states with a total of 570 patients treated with diamorphine therapy. This was a small proportion of the 75 400 patients in ORT in Germany at the time [18]. Nussbaumstrasse Substitution Clinic, which belongs to the Ludwig Maximillian University was the only facility which provided diamorphine therapy in Munich at the time of the study. Diamorphine converts to an active metabolite that binds to the receptor with a half- life of around 3 hours. The feeling of euphoria occurs around 10-20s after it passes the blood- brain barrier, lasting for around 10- 30 minutes. The treatment is highly structured and demanding requiring 2-3 daily administrations in intravenous form with a daily maximum dose of 1000mg under strict medical supervision. The symptoms of overdose are that of opiate usage; being respiratory depression, miosis, and coma. The selection criteria for diamorphine therapy in Germany is very strict, including evidence of concurrent intravenous drug use; an under performance of functioning in psychological and/or social domains, and at least 2 unsuccessful ORT also known as 'methadone non-responders' lasting for at least 6 months. It is thought that some patients who do not tolerate the effects of methadone might benefit from diamorphine and it also prohibits patients from consuming street heroin, hence reducing risk associated illnesses [19, 20].

1.1.3 Opiate overdose

Until the late 1990's in the United States of America (U.S), the main cause of opiate overdoses has been from heroin. As a result of the rapid increase in prescription opiates for the treatment of chronic pain, there has been an increase in opiate overdose deaths by almost 36% in the U.S between 2000- 2012 [21]. Moreover, there there has been a rise in the use synthetic fentanyl, which is a significantly more potent opiate compared to heroin. In a report by the German Federal Criminal Police Office (Bundeskriminalamt), the number of opiate overdoses, including from prescription opiates has been steadily declining since 2008. In 2011, there were 1.4 drug-related deaths per 100,000 inhabitants in the state of Bavaria. The highest numbers of deaths per inhabitant in Germany were in Berlin and Hamburg, being 3.3 and 3.2 per 100,000 respectively. There has been a drastic reduction in the number of single heroin/morphine overdoses by 57% from 2010 to 2011 (529 vs 279), with the number of poly-drug overdoses also reducing but overtaking the number of single heroin/morphine overdoses. Around 23.7% of all opiate overdoses in Bavaria involved methadone, whereas only 0.6% involved buprenorphine. Moreover, since 2012 there has been a rise in fentanyl- related deaths in Bavaria from 36 to 50. The most common cause of fentanyl overdose is in combination with other opiates followed by alcohol [22]. Opiate overdoses are treated in hospital settings, as well as in the community with naloxone, which is a potent opiate antagonist highly effective in reversing the clinical effect of opiates. It

can be given in diverse routes, but its effect is short acting and often multiple doses need to give to achieve sustained effect. Since most of the overdoses occur in private spaces and are witnessed by others, many programs around the world have been developed to give naloxone to drug users and their families with the aim of reducing opiate related deaths. As of 2002, Berlin offers Take Home Naloxone Programmen (THN) where Naloxone Notfall-Kits, initially in intramuscular form, then years later also as nasal applicators, were distributed among the opiate addicted population. The use of take-home naloxone by laypersons in currently over 20 countries has demonstrated the ability to reverse the effects of opiates appropriately, safely in case of overdose, as well as being cost-effective in reducing emergency admissions [23].

However, with the recent rise in poly-pharmacy overdoses, naloxone should only be used outside of hospital settings with considerable caution. In a retrospective study conducted by the University of Virginia analyzing calls made to the U.S poison centers from 2000-2016, it showed that there was a 4- fold increase in the number of cases where naloxone was used in pre-hospital settings in cases of suspected opiate overdose either by the paramedics or non-medical personnel. There was a fatality rate of 1.5% and a further 22.7% of all cases with major medical outcomes during the study period. 59% of cases were due to multiple substance exposures with benzodiazepine as the most common co-occurring substance [24]. With the increase usage of benzodiazepine in cases of suspected pre-hospital overdose, it is important to note that naloxone can be more harmful than good in many cases, as it can lead to pulmonary edema and cardiac events in patients who might not have used opiates. Moreover, it provides only a partial improvement in the level of consciousness in patients with mix intoxications. In particular, it increases the risk of aspiration in patients who might be still partially sedated from benzodiazepine usage, with the additive effect of benzodiazepine impairing the gag reflex.

1.2 Benzodiazepine abuse among ORT patients

1.2.1 Classifications and Pharmacology of benzodiazepines

Benzodiazepines were first introduced into clinical medicine in 1960 and along with barbiturates, they act predominantly to inhibit the GABA receptors in the central nervous system (CNS) to produce anxiolytic and sedative effects. Benzodiazepines have a much higher safety profile compared with barbiturates [25]. Benzodiazepines are metabolised in the liver by cytochrome P450 system into active forms. Half- lives of different benzodiazepines can vary from 24-48 hours.

1.2.2 Indication of general usage of benzodiazepines

World-wide benzodiazepine is commonly prescribed in the hospital and by general practitioners in the following clinical settings [26]:

- Treatment of "breakthrough" symptoms of anxiety disorder during acute phases whilst other treatments are being initiated;
- Insomnia for the intentional use of less than 2 weeks;
- Muscular spasms in acute lower back pain;
- Epilepsy to control seizures activity in acute settings;
- Control of withdrawal symptoms such as in alcohol dependency; and/or
- An anaesthetic induction agent for its anxiolytic and amnesic properties.

1.2.3 Side -effects and addiction

Misuse of benzodiazepine can cause sedation, psychomotor impairment, memory problems namely anterograde amnesia, and decline in attention and concentration [27]. Tolerance to benzodiazepine tends to develop after 2-4 week. Most of the symptoms from benzodiazepine discontinuance normally occur 3 days after discontinuation, reaching the highest intensity within 2 weeks and subsiding in 4 weeks. The duration of the symptoms typically depends on the half-life of the benzodiazepine. These symptoms include anxiety, insomnia, tachycardia, hallucinations and tremor. In Germany, benzodiazepine is prescribed frequently by general practitioners, psychiatrists, as well as after hospital admissions aimed for outpatient usage as required in the short-term mostly as an anxiolytic or muscle relaxant. There has been a problem world- wide with the so-called 'doctor shopping' for narcotics and psychoactive substances such as benzodiazepines. This involves the patients requesting prescriptions from multiple practitioners simultaneously without informing the practitioner of the other practitioners involved. In addition, benzodiazepine can be obtained on the illicit drug market and through the Internet.

In Australia, it is estimated that around 35% of all medications obtained by doctor shoppers are benzodiazepines [26]. In both Australia and many states in the U.S, computerised systems such as the Prescription Shopping Program Australia wide and the Prescription Monitoring Program in Virginia, U.S have been implemented to help doctors to identify drug seeking patients and prevent double prescriptions of such substances.

1.2.4 Benzodiazepine abuse among ORT patients

Benzodiazepine usage has been observed extensively among heroin users across many countries. It has been found that intravenous drug users who also abuse benzodiazepine are associated with a higher level of risk-taking behaviours, other poly-drug use, heroin overdose, poorer clinical state and psychosocial functioning than those intravenous drug users who do not [28, 29]. Heroin users tend to inject crushed benzodiazepine tablets. This can also lead to injection associated morbidities such as infections, thrombophlebitis, as well as increased mortality by further depressing the central nervous system and respiratory functions. Benzodiazepine has also been shown to increase the opiate serum concentration in patients with impaired hepatic functions [30], thus affecting those patients with hepatitis or alcohol- induced cirrhosis. Benzodiazepine misuse has been found in 30 to 50% of ORT patients in Europe [25, 31]. The aim for illicit co-use of benzodiazepine by opiate users can be varied. It can be used by heroin addicts to self-medicate opiate withdrawal symptoms when heroin is not available or when trying to reduce consumption. Benzodiazepine when used together with opiates can minimise its unpleasant excitory effect and in higher doses can enhance the euphoriant effects of psychostimulant [25]. For this reason, patients in ORT may misuse benzodiazepines to enhance the effect of their substitution medications. The misuse of benzodiazepines in this case might also be due to the sub- optimal dosing of the ORT or due to self- medicating their psychiatric illnesses. These aspects will be explored and discussed later in the thesis.

1.2.5 Death related to benzodiazepines

Benzodiazepine intoxication effects can occur at plasma concentrations of >1.5mg/L [2]. Single benzodiazepine overdose requires only supportive therapies and is rarely life- threatening. Benzodiazepine intoxication mixed with alcohol and opiates can however, cause respiratory and CNS depression which in turn leads to a higher risk of death by overdose. The most common types of benzodiazepine involved in drug related overdose deaths in Europe are benzodiazepines with a rapid onset of action such as diazepam and alprazolam [25]. Benzodiazepine has been post-mortem identified in 40-80% of methadone related deaths in France, U.S and Australia and in 50-80% of heroin related deaths in Germany, Ireland and the U.K . Moreover, counterfeit diazepam tablets have been seized in Europe containing also potent synthetic opiates which poses a higher risk of overdose [25].

1.2.6 Antidote

Intravenous flumazenil might be used to rapidly antagonise the effect of benzodiazepine in situations of coma. This should however be used with extreme caution in patients who have high benzodiazepine dependency as it can precipitate in withdrawal symptoms including seizures. The risk is especially increased if another pro-convulsant such as tricyclic antidepressants [26] is also used. It also has a short half- life so often multiple doses have to be given especially in combination with overdoses involving long- acting benzodiazepines.

1.3 Psychiatric co-morbidities among ORT patients

In this study, we have mainly explored 2 psychiatric co-morbidities commonly present in patients who receive ORT, being insomnia and depression. These illnesses impact significantly on the overall functional status of these patients and the effectivity of ORT. In this section we will discuss each in detail and some of the current strategies clinicians have used to combat them.

1.3.1 Definition and epidemiology of insomnia in the general population

Insomnia is a major health issue in the western world and it can lead to significant physical, social and psychological damages. It is defined as a disorder characterised by an inability to maintain sleep continuity, early morning awakening, and impairment of daytime functioning [32, 33]. Almost half of all adults in the western world report sleeping disturbances and 15-20% suffer from chronic sleeping dysfunction [34]. Chronic insomnia is defined as difficulties in initiating and maintaining sleep for at least 1 month resulting in daytime impairment [35]. Chronic insomnia is also associated with a higher risk of developing somatic disorders and substance abuse. Those with chronic insomnia tend to have persistent symptoms after a year of diagnosis [36]. Those with a subjective perception of serious insomnia tend to be in populations of older age, female, divorced or widowed; they tend to have known multiple physical co-morbidities and psychiatric illness and are likely to display higher levels of anxiety and depressive symptoms [32, 37].

1.3.2 Common general causes of insomnia

Many factors can contribute to sleep dysfunction, most important of which being medications, drug or alcohol abuse, psychiatric illnesses, a multitude of medical conditions and social factors. All of these factors need to be considered and addressed before starting treatment in patients with chronic insomnia.

1.3.3 Substance- induced insomnia

Substance- induced insomnia is characterised as disruption of sleep and adverse daytime consequences from the use of illicit substances, prescription medications or licit substances such as caffeine and alcohol. Illicit substances, which commonly lead to insomnia, include marijuana, cocaine, opiates and sedatives – hypnotics such as benzodiazepines and the non-benzodiazepine Z- drugs [38]. The prevalence is found in roughly 0.2% of the population [39] and approximately 75% of the ORT population [38]. One can have insomnia before developing substance abuse or as a result of it. In ORT patients, this can be especially difficult to distinguish, as the majority of patients co-use illicit substances and possess risk factors that can contribute to poor sleep quality. Sleep dysfunction in this group of patients has been linked to impairment of quality of life, psychiatric complaints and the increased

use of illicit substances [38]. Substance use can impact on sleep by either increasing or decreasing arousal [38]. Opiates, such as morphine, heroin and methadone are known to be disruptive to the sleep cycle. They are shown to reduce Slow-wave sleep (SWS) and Rapid eye movement sleep (REM). Symptoms of insomnia may also result from opiate- induced apnoea, in which, opiates suppress the central respiratory drive, as well as impairing the upper airway muscle functions [40]. Sleep -related withdrawal symptoms might also occur after reducing or stopping substance use after a prolonged period of time. One study has shown that patients could improve their sleep after initiating the use of buprenorphine plus naloxone (Suboxone) [41], however, another study showed that that the degree of sleep impairment did not vary significant between methadone and buprenorphine patients but more based rather on the other psycho-social factors [42]. The main factors which cause therapy resistant chronic insomnia in this patient group include pain, depression, substantial stress, benzodiazepine and nicotine usage [38, 42].

1.3.4 Effect of benzodiazepine on opiate induced insomnia in ORT patients

The length of sleep time demonstrated in sleep studies is prolonged with benzodiazepine use in ORT patients [38], but it is also associated with the increased risk of central apnoea, leading to aspiration and overdose. Many patients in this group use benzodiazepine to initiate sleep [30]. Discontinuation of benzodiazepines can cause withdrawal symptoms leading to anxiety, agitation and insomnia.

1.3.5 Treatment of substance- induced insomnia

General treatment of insomnia involves primarily identifying and treating the underlying medical and psychological causes. Patients with substance- induced insomnia are best treated in addiction centres. The first step is to identify and reduce illicit drug abuse. Non-pharmacologic interventions for insomnia consist primarily of short-term cognitive-behavioral therapies, and improvement in sleep hygiene.

1.4 Depression

1.4.1 Definition and epidemiology

Major depression is a common illness which burdens psychosocial functioning. The lifetime risk of depression in developed countries is predicted to be between 15-18% [43] and this has been estimated by the World Health Organization (WHO) to become the number one burden of disease by 2030 [44]. The Diagnostic and Statistical Manual of Mental Disorders (DSM- 5) criterion has been used world-wide in the diagnosis of major depressive disorder. The individual must be experiencing at least 5 or more of the symptoms listed in the criterion nearly every day during the same two-week period. This is normally accompanied by functional impairment depending on the severity of the symptoms. For the diagnosis of a depressive episode, at least one of the symptoms presents must be either having a depressed mood or the loss of interest or anhedonia [45]. The diagnosis of depression among the ORT patients can be much more difficult because similar presentation of symptoms often occurs in other psychiatric disorders and medical illnesses, as well as a result of substance abuse or withdrawals.

1.4.2 Epidemiology among the opiate addicted population

Depression is a common problem along drug users, with the rate of lifetime prevalence of major depression in opiate dependent patients enrolled in ORT programs to be in the range of 20% to 50% [46]. As a result of the complex relationship between depression, drug dependence and various psycho-social stress factors, the prognosis have been poor among drug addicted patients. ORT therapies have been associated with an improvement in depression [46]. Suicide in ORT patients is much more prevalent compared to the general population and there are many factors which could help us to identify patients at risk. According to a study done at the Yale University Drug Dependency Unit involving around 500 ORT patients, the lifetime suicide attempts among the subjects are 4 times higher than the community population. Suicide attempts are more likely in patients with depression, schizophrenia, and borderline and narcissistic personality disorders. Subjects with suicide attempts have a mean Becks Depression Index (BDI) score of 13, compared to a score of 9 of those without. Results suggest that factors significantly contributing to suicide attempts among the ORT patients include being from a lower socioeconomic class being females, lack of education, unemployment, being separated or divorced, family history of depression and alcoholism, as well as, childhood family disturbance and abuse [47]. In another similar study involving more than 400 ORT patients in New jersey, 39% of their subjects have had at least one suicide attempt. Similarly, a significant percentage of these patients were females, have endured childhood abuse, and have a family history of suicide and drug abuse [48].

1.4.3 Management

The treatment of depression involves psycho- and pharmacotherapy. It is also crucial to stop drugs that can cause a depressive mood, address concurrent substance abuse and promote better sleep patterns as well as a better diet and exercise. In most cases, a combination of psychotherapy and medications are needed to treat the symptoms. In rare cases, electroconvulsive therapies can be used in non-responders [45].

Psychotherapies

Many clinical trials have shown that several forms of psychotherapies are effective in the treatment of depression, including cognitive behavioral therapy, behavioral activation therapy, interpersonal psychotherapy and problem-solving therapy. It has been shown that these therapies are about equally effective as pharmacotherapies for depression and that the combination of psychotherapy and pharmacotherapy is more effective than either one alone [49]. Cognitive behavioral therapy and interpersonal psychotherapies are the most widely used. Cognitive behavioral therapy focuses on how to address negative thoughts and replace them with more positive ones [45, 49], and interpersonal therapy concentrates on solving conflicts in interpersonal relationships and improving social interactions [45].

Pharmacotherapies

Antidepressants are typically effective in moderate to severe depressive episodes [45]. Most antidepressants act to alternate monoaminergic transmission at the receptors, namely by increasing the transmission of serotonin, norepinephrine and dopamine within the brain. There are 5 major classes of antidepressants. These are Selective Serotonin- Reuptake Inhibitors (SSRIs), Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs), Tricyclic Antidepressants (TCAs), Monoamine Oxidase Inhibitors (MAOs) and atypical antidepressants. The first line therapy used in most developed countries is SSRIs due to its better tolerated side effect profile compared to other groups of antidepressants [50]. Ultimately the type of antidepressant is chosen for the symptoms the patients presents with, the patient's compliance and other co-morbidities and their tolerance to the side effects of the medication. In opiate substituted patients, it is also important to consider the interactions between the ORT and the chosen antidepressant before commencing therapy. For example, the use of both TCAs and methadone can prolong QT intervals and lead to cardiac arrhythmia.

1.4.4 Use of benzodiazepines in the treatment of depression

Benzodiazepine have been prescribed for patients with depressive disorder to relieve symptoms of anxiety and insomnia. It has been estimated that across the U.S and Europe around 40% of patients with depression have been prescribed benzodiazepine by either their primary care physician or psychiatrist [51]. It has also been strongly recommended by guidelines to limit the use of benzodiazepine to less than 4 weeks [52], due to risk of addiction, as well as its negative effects on mood and cognition. Chronic benzodiazepine

users also exhibit more severe symptoms of anhedonia, higher anxiety levels and an overall lower occupational functioning and thus, limiting their chances of positive outcomes from depression compared to non- benzodiazepine users. In addition, the majority of the subjects have abused benzodiazepine in conjunction with SSRIs and SNRIs [51]. This might be due to the less sedative effect of these groups of antidepressants compared to older groups of antidepressants [53]. In the context of opiate abuse, not only is use of benzodiazepine particularly dangerous due its increased risk of drug overdose, but it also promotes the notion of self-medicating the symptoms of depression instead of seeking therapy. The symptoms of anhedonia caused from high levels of benzodiazepine abused by these patients can also pose difficulties in the diagnosis and treatment of depression.

1.5 Medical consequences of opiate addiction

Opiate addicted patients suffer not only from a complex array of psychosomatic disorders, as well as many chronic medical illnesses. These illnesses could either be the direct consequences of opiate addiction, or as a result of an unhealthy lifestyle from the lack of health awareness and from years of inadequate medical attention. Generally, the chronic illnesses these patients are likely to suffer from include, Chronic Airway Diseases such as COPD from chronic nicotine abuse, Diabetes Mellitus and peripheral and cardiovascular diseases from obesity and the lack of exercise. Specific medical conditions resulting from opiate addiction include, bowel complaints, chronic pain syndromes, blood-borne infections such as hepatitis B, hepatitis C and HIV, as well as, localised and systemic infections from injection sites. People who use heroin have higher rates of motor vehicle accidents compared to the general population [54]. However, patients maintained on methadone or buprenorphine have not shown significant deficiencies in tasks related to driving performance when not using illicit drugs [55]. In this study, we have looked at how hepatitis C and chronic pain syndromes have affected the quality of life of ORT patients.

1.5.1 Hepatitis C

Hepatitis C virus (HCV) infection is a common cause of chronic liver disease, leading in many cases to cirrhosis, decompensated disease, liver cancer and death [56, 57]. As of 2015, it is estimated that around 300,000- 500,000 patients in Germany suffer from chronic hepatitis C infection. 8 out of 10 patients with HCV with a known mode of transmission were linked to intravenous drug use. Between 37-73% of patients who inject drugs in Germany have been found to have HCV antibodies [2]. Although the study of Hepatitis C has not been the main focus of our study, it has been important as well as interesting to observe the physical and psychosocial impact that the burden of cirrhosis has had on the quality of life of ORT patients. The symptoms of cirrhosis have been one of the causes of chronic pain in the subjects which ultimately affected their mood and sleep quality. Despite the significant morbidity and mortality of the disease, it is estimated in the U.S in 2013 that out of the 3.2 million Americans who have chronic HCV infections, only 7 to 11% have been or are being treated, and 5 to 6% have had successful clearance of the virus [57]. One of the key contributors to this low uptake of treatment has been associated with the poor tolerance of the standard Interferon therapies, with severe side effects such as fever, flu-like symptoms, leukopenia, thrombocytopenia and depressive symptoms, just to mention a few [58]. One of the topics of interest in Addiction Medicine and Hepatology in the last few years has been the new developments in the treatment of Hepatitis C. Since 2015, the new oral direct acting antiviral (DAA) treatments for HCV have been available in Germany. The current treatment allows for most patients to be treated successfully, regardless of the presence of cirrhosis, HIV, hepato-renal disease and previous therapies [59]. They are better tolerated due to lesser side effects and has shown to be much more effective than the interferon therapy with cure rates of >90% [60]. The typical regimen are 8- 12 weeks in duration with a once daily combination pill. Presence of cirrhosis or a high viral load might

warrant a longer treatment period or with the addition of ribavirin [59]. Other factors in the poor involvement of treatment include lack of referrals of patients to HCV providers for therapy, lack of patient compliance, poor understanding of the new therapy and fear of its side effects.

1.5.2 Chronic pain

Chronic pain is a complex physiological illness with psychosocial effects. It can severely impact on the general well-being of the patient and can present together with symptoms of depression and insomnia. It is defined as pain lasting longer than 12 weeks and has been estimated to affect 18% of the general population of Europe [61]. The opiate addiction crisis can be partly blamed on the overprescription of opiate medications from health practitioners for chronic pain. In the U.S some 3-4% of the adult population with acute pain were prescribed opiates for longer than 3 weeks [62].

Epidemiology in opiate- addicted patients

Chronic pain is common in ORT patients. It can originate from infections from injection sites, poor wound care, polyneuropathies from diabetes mellitus, alcohol abuse and vitamin deficiencies. Chronic back pain is also common from disc prolapses due to the laborious nature of some of the patients' jobs. Furthermore, ORT patients have a high rate of accidents and injuries, as well as severe burn injuries. In combination with poor nutrition, hygiene, and treatment compliances in this patient group, they are at high risk of developing tissue healing disturbances and thus, chronic pain syndrome.

Opiate- induced hyperanalgesia

Some studies have further shown that many ORT patients have developed signs of opiate - induced hyperanalgesia, which is heightened pain sensitivity after prolonged period of exposure to opiate agonists [63, 64]. Clinically hyperanalgesia can cause an inappropriate increase in the dose of opiates which further exacerbates the pain [62]. It has also been observed in a study that the pain has been reported in 44.9% ORT patients after some undefined period following the commencement of ORT, who reported not to have pain at the beginning of methadone treatment [65]. Patients on methadone therapy with chronic pain have an increased level of inflammatory markers, which could increase their sensitivity to pain [66].

Management

Management of chronic pain begins with the history and physical assessment of the different types of pain, identifying the psychosocial factors which might contribute to the pain, and the functional and emotional burden of the pain. Treatment normally involves a multi-modal approach including physical therapy, cognitive- behavioral therapy, surgical interventions, analgesia and neuro-stimulation therapies [62]. The choice of analgesia

typically starts with the WHO analgesic ladder, starting from simple over- the- counter analgesics such as Paracetamol and NSAIDS then climbing the ladder to medications such as opiates, antidepressants, steroid, anticonvulsants if the pain is still present. Often a number of different pharmaceutical agents are used to act at differing pain receptor sites. The management of chronic pain in opiate-addicted patients is unfortunately far more challenging and complex. Doctors must balance adequate pain control with limited and controlled usage of opiates, taking into considerations the risk of addiction, overdose and drug interactions. ORT patients have an initially higher opiate tolerance and this, compounded with their often delayed and serious medical presentations, and the phenomenon of opiate induced hyperanalgesia, makes it difficult to provide satisfactory pain control. Furthermore, clinicians are oftentimes reluctant to provide opiates or strong pain medications with abusive potential even in acute settings to these patients, because they are unsure of the long-term consequences. This is a vicious cycle leading to the patients fear of under treatment for acute pain in hospital and promoting self- medicating and delays in seeking medical attention. This will be further discussed in later sections of the thesis. Aside from physical interventions, there has been research in developing opiates with non-addicting potential, and the use of therapeutics that antagonize the inflammatory pathways, such as tumor necrosis factor (TFN) inhibitors just to name a few [67]. In cases of opiate -induced hyperanalgesia, slowly tapering the dose of opiates can be helpful in managing the pain [62].

1.6 Social consequences of opiate addiction

Opiate addicted patients typically present with many social issues. These include unemployment, financial debts, homelessness and relationship troubles. European Monitoring Center for Drugs and Drug Addiction (EMCDDA) reports 302,594 drugs- related offenses in Germany in 2016 [2]. Aside from decreasing the overall mortality of opiate addicted patients, one of the main aims of substitution therapy is to improve the overall quality of life of the patients. This includes continuously addressing legal and social issues during the course of the treatment.

1.6.1 Unemployment

Unemployment is one of main issues affecting ORT patients. It can lead to psychosocial impacts such as low self- esteem, depression, financial troubles, and consequently, reinforce drug use and commitment of petty crimes. Attending a regular job helps patients to establish a daily rhythm, which would also help them to achieve and stabilize drug abstinence in the course of ORT. The labor market is not easily accessible to drug- addicted patients. Firstly, these patients tend to have lower school and vocational qualifications, as well as criminal records typically from a younger age. Secondly, there are immense negative attitudes and beliefs towards the patients on the part of employers. In 2005, Germany introduced "One- Euro Jobs", helping people to improve their employability and to help employers to check whether the unemployed person is suitable for the role. This has helped long-term unemployed patients by providing them with a task and a daily routine, as well as testing their willingness to work [68]. In substitution clinics, there are social workers supporting employment and further vocational training of these patients.

1.7 Objectives of the study

The aim of the study is primarily to identify the impact of ORT on depression and insomnia in the subjects represented through the BDI-II and PSQ scores. We also analyzed the pattern of benzodiazepine usage among these patients, especially in relation to those who have been diagnosed with depression and anxiety, as well as in patients with severe insomnia. Finally, we focused on how chronic somatic illnesses, such as chronic pain syndrome, as well as how social factors such as unemployment can affect ORT patients' mood and sleep qualities.

Kapitel 2

Method

This cross-sectional study was conducted from September to November 2015 in Munich, Germany. The two centers chosen for the study were the Westend Substitutions Practice (WSP) and the outpatient department for Opiate Maintenance Treatment on Nussbaumstrasse (NBC). Germany had a population of 82 million people in 2015, with 1.43 million living in Munich. It was difficult to estimate the total number of patients in ORT in Munich at the time of the study. EMCDDA reports that 78,500 patients were in ORT Germany-wide in 2016 [2].

2.1 Institutions involved in the Study

2.1.1 Westend Substitutions Practice (WSP)

WSP is an opiate substitution center located on Bergmannstrasse 13, in the suburb of Schwanthalerhoehe- Laim in Munich. The center was built up by several general medicine doctors and runs in parallel with a family medicine practice. The ORT used in the practice included methadone, levomethadone and buprenorphine. There was a total of 120 patients at the time of the study and the majority were being treated with methadone. The practice had a social worker on site, who provided assistance with employment, housing and issues regarding finances and relationships. They also worked closely with several local psychiatrists to refer patients for continuous assessment and psychotherapies. Urine tests were carried out on a random basis to check for illicit drug use.

2.1.2 Nussbaumstrasse Substitutionsambulanz (NBC)

NBC, also known as Substitutionsambulanz N5 is located on Nussbaumstrasse 5, in the centre of Munich. It is a part of the Ludwig Maximillian University hospital's department for psychiatry and psychotherapy. The majority of patients had received levomethadone. They offer injectable diamorphine in addition to the other ORT. There was a total of 150 patients treated in NBC at the time of the study, 50 of which received diamorphine therapy. NBC is a part of a Germany-wide project (www.heroinstudie.de) and they are

the only ORT clinic in Bavaria which offers diamorphine therapy. Furthermore, they have participated in many research projects further developing substitution therapy in Germany. Most of the patients in NBC also suffer from severe psychiatric illnesses in addition to opiate addiction. Many of them have been referred by the small substitution clinics if the patients are difficult to treat due to their psychiatric illnesses, social situation, non-compliance, heavy drug abuse or refractory response to the standard ORT. They are generally being reviewed by the doctors and social workers once a week and many are being treated by in- hospital psychiatrists in addition to receiving ORT. The patients in NBC also tend to be in a poorer general state of health compared to the patients who attend practices. Their daily attendance and illicit drug consumptions are strictly monitored. Patients who suffer from acute infections and wounds are promptly assessed and treated in the medical clinics which are ran four times a week. The Ambulance is also within proximity of the LMU inner-city hospitals for internal medicine and surgery, so that patients can easily be transferred for in-patient treatments.

2.2 Structure of the study

The study included a total of 113 patients from the two facilities who received either methadone, levomethadone, buprenorphine or diamorphine as treatment for their opiate dependence. It was conducted over a period of 3 months under one-on-one supervision in the participating facilities. The questionnaires were filled out together with the observer normally shortly after the subject received their daily dose of ORT to reduce the impact of withdrawal symptoms.

Prior to filling out the questionnaires, the subjects were explained in detail the purpose of the study, how the results will be used, and that their confidentiality will be maintained throughout the study. The questionnaires were anonymous and the subjects were assigned a case number and the facility where they were treated was also marked. They were also informed that some of their information, such as their past medical history, treatment records and urine drug screening results might be obtained from their existing files. Participation in the study was entirely voluntary. Consent to participating in the study was given verbally. Prior to commencing the study this was approved by the LMU ethics committee.

2.3 Questionnaires

The questionnaire was designed by the principle investigators specifically for this study. They took on average 30 minutes to complete with the subjects and results were checked directly after completion. Any unanswered questions were explained to the patients and were marked for calculation purposes if the subjects intentionally did not want to answer. Many questions would often have to be explained to the patients as many had non-proficient literacy skills. After obtaining the consent, general patient data was gathered. This included the patient's age, gender, BMI, and the type, and dosage of their current ORT. Further

questions specific to the following areas were then asked.

2.3.1 Alcohol and illicit drug use

Patient's self-reported current alcohol and illicit drug use were documented, with the amount and route of consumption being either oral, nasal or intravenous. Drugs abused by the subjects were heroin, cocaine, marijuana, benzodiazepine, amphetamine, pregabalin, fentanyl and mephedrone, also known as Badesalz on the black market. For the interest of this study, patients who admitted to benzodiazepine usage were also asked the amount, type and source of the current usage. It was particularly interesting for us to see whether they had obtained the benzodiazepines through a prescription or on the illegal market. Furthermore, urine analysis results for benzodiazepine up to the last one month of the study were checked in the patient files and those with positive results were recorded for the study. The different benzodiazepine usages were converted to diazepam equivalent doses in milligrams using the scheme adapted from the Ashton Benzodiazepine Equivalence Table - `https://www.benzo.org.uk/bzequiv.htm`.

2.3.2 Psychiatric history

A detailed known psychiatric history was documented and cross checked with the patients' files. This included the formal diagnosis of their psychiatric illness, past and on-going psycho- and pharmacotherapies. The type and dosage of the psychoactive medications were noted, and when possible the source of the medication noted, whether it was prescribed by psychiatrists, general practitioners and/or obtained illegally. Suicide attempts, and family history of psychiatric illnesses, specifically depression was documented.

Chronic co-morbidities

Somatic co-morbidities, such as those attributing to poor sleep qualities and depression were asked. These included diagnosed sleep apnea (with or without the use of C-PAP machine), chronic pain syndrome, restless leg syndrome, peripheral neuropathies secondary to either vitamin B12 deficiency in alcoholism or in diabetic patients, cardiac insufficiency, and respiratory illnesses such as asthma or COPD. Blood-borne infections secondary to intravenous drug use including hepatitis C and HIV were noted, as well as their previous and current treatment, known liver cirrhosis, and if they are known to have been cured of the hepatitis C virus. A known current medication list was also documented.

2.3.3 Social factors

A number of questions were designed to analyze the social demographics of the subject group. These included the following:

- patient's completed education level, divided into 3 categories according to the German school system being Hauptschule, Realschule and Gymnasium;

- completed apprenticeships and vocational training;
- current financial debts;
- current employment, number of working hours, shift work schedules and their job satisfaction;
- length of unemployment, and the type of social benefits they are receiving
- current accommodation arrangements, either if they are renting their own apartment, receiving government housing, sleeping in a caravan, or being homeless. Government housing or Pension is a common type of housing provided by the German government to people in difficult social and financial situations. This type of housing commonly accommodates many people of the similar socioeconomic background and is, at most times poorly maintained and crowded. The patients often have a lack of privacy and this can consequently impact on their sleep quality;
- civil status being single, married, separated, divorced or widowed;
- whether they had any children;
- interests and hobbies.

After the completion of the questionnaire, Becks Depression Inventory II, Fragerstrom test for nicotine dependency and Pittsburg sleeping scalar were given separately to the subject, to assess for depression, nicotine dependency and sleeping disturbances respectively.

2.4 Becks Depression Inventory II

The Becks Depression Inventory II (BDI-II) is a self-evaluation tool for the detection of depression in persons > 13years of age [69]. It measures the severity of the depression, corresponding to the non-somatic criteria for the diagnosis of a major depression according to DSM-5. These relate to the following cognitive and affective symptoms including: mood, pessimism, sense of failure, self-dissatisfaction, guilt, punishment, self-dislike, self-accusation, suicidal ideas, crying, irritability, social withdrawal, indecisiveness, body image change, work difficulty, insomnia, fatigability, loss of appetite, weight loss, somatic preoccupation, and loss of libido [70, 71]. The BDI-II is a revised version of the BDI, with slightly different questions and cut off scores. The questionnaire consists of 21 questions and each question is ranked in terms of severity and scored from 0 to 3. The score ranges between 0-63. For interpretation 0–13 represents minimal depression, 14–19 mild, 20-28 moderate and 29-63 severe depression [72]. However, the patients involved in this study suffer from drug addiction and most suffer from chronic illnesses, such as chronic pain, infections, cardiovascular and respiratory illnesses, often with poor treatment compliance. Thus, it can be difficult using this current inventory to screen for depression in these patients, as scores given in BDI-II to somatic symptoms such as insomnia, loss of appétit,

weight loss, etc can occur in medical illnesses and chronic drug addiction but also overlap in depression [73]. As a result, a higher cut off score has been suggested for these patient groups [71] or an alternative Becks Depression Inventory Fast Screen [69], where scores are given to cognitive and affective symptoms, omitting somatic features. This will be further discussed later on in the thesis.

2.5 Pittsburg Sleep Quality Assessment

The Pittsburg Sleep Quality Assessment (PSQ) is a self- rated questionnaire that assesses sleep quality over a 1-month time interval. It consists of 19 questions and this is then subdivided into 7 components, those being, subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction [74]. It was developed in 1988 [75] and provides a quick, easy, reliable way of assessing and interpreting patients' sleep quality. The cut-off global score of equal to 5 has been used to distinguish between good and poor sleepers. The sensitivity and specificity of PSQ in assessing primary insomnia has shown to be 85.7% and 86.6% respectively [76]. The main limitation of PSQ, much like BDI-II and other self-evaluation questionnaires is that it is highly subjective and the score depends on the patient completing them. The often misinterpretation of the questions can lead to a falsely high or low score.

2.6 Fragerstrom Test for Nicotine Dependence

The Fragerstrom Test for Nicotine Dependence is an evaluation of one's nicotine dependency. It is a short questionnaire consisting of only 6 questions, with a total score of 1-2 indicating low dependency and >8 indicating high dependency [77]. Although test results of the Fragerstrom evaluation have not been discussed in detail in this thesis, further analysis could be conducted in future studies focusing on the role of nicotine dependency in multi-substance abuse, as well as the effectivity of Nicotine Replacement Therapies in this patient group.

2.7 Inclusion criteria

The inclusion criteria for patients included the following:

- over the age of 18 years;
- a positive diagnosis of opiate dependence according to ICD 10 criterion;
- ability to give voluntary consents;
- regular attendance to the substitution clinic;
- a blood alcohol level of <0.049 g/dL at the time of receiving their daily dose

- not obviously under the influence of illicit substances
- stable cognitive and psychiatric conditions at the time when the questionnaire was conducted

2.8 Method of analysis

For the statistical analysis, we split the patients from both clinics into 4 groups according to their current ORT scheme, those being methadone, levomethadone, buprenorphine and diamorphine. We used counts, percentages and means to summarize the main patient demographics, such as their age, BMI, length of therapy, level of education, current type of accommodation, their co- morbidities etc. Similarly, we assessed patients with a positive diagnosis of depression and/or anxiety and calculated the fraction of patients from this group who are still undergoing active psycho- and/or pharmaceutical therapies, as well as the groups of psychoactive medication used for treatment. We then looked at the number of patients with concurrent use of alcohol and illegal substances and in particular, the types and mean dosages of benzodiazepine use.

For the purpose of calculations, we allocated dose of benzodiazepine usage in milligrams of diazepam; PSQ and BDI-II scores as continuous variables; the 4 groups of ORT as sub-variables; and gender, BMI, unemployment, self- reported chronic pain and sleeping arrangements as co-variables. We used binary logistic and multi-linear regression models to investigate the interactions between the continuous variables. We then used Pearson's Chi Square test to identify associations between sub- variables and co- variables. Independent Sample T- test was employed to find relationships between the co- variables and mean BDI-II and PSQ scores. Furthermore, ANCOVA was used to analyze the impact of the co-variables on BDI, and PSQ scores in presence of positive urine analysis of benzodiazepine use. The dose of benzodiazepine use was not controlled in this case.

We used One-Way ANOVA to compare the mean scores of BDI, PSQ, and the mean consumption dosage of benzodiazepine from the participants with mean dosage of each of the sub-variables. We then further ran the Post- HOC analysis to look at the relationships between the groups.

Benzodiazepine usage was divided into 3 sub- groups, those being legal, through prescription by health professionals; illegally obtained on the black-market and those who use both sources. The T- test was used to find the source of proposed benzodiazepine usage for the treatment of insomnia, as well as the concomitant self-treatment of depression and/or anxiety in the subjects studied. The mean dosage of benzodiazepine in each of the sub-groups was calculated against the mean BDI-II and PSQ scores. The results were calculated using SPSS version 24 and P values less than 0.05 were considered significant.

Kapitel 3

Results

3.1 Data

3.1.1 Patient structure

There was a total of 113 patients who participated in the study, with 65 patients from WSP and 48 from NBC. 78% of the patients who participated were male, with mean age of 41 years, and had a mean BMI of 24. A total of 30 patients were taking methadone, 50 levomethadone, 18 buprenorphine and 15 diamorphine. As shown in the graph below, a higher percentage of patients were on levomethadone in NBC compared to WSP and there are no patients in NBC who were on methadone therapy. As mentioned previously, NBC is also the only clinic in the state of Bayern that offers diamorphine therapy. Patients have been in substitution therapy for a mean of 10.6 years.

3.1.2 Drug abuse profile

Among the patients who participated in the study, the mean age of first contact with illicit substances independent of alcohol was 16 years. Patients have reported that this was mainly through their direct social environment. 45% of patients have had partners or family members also suffering from drug addiction and a few patients at the WSP have also had partners died of illness directly related to drug abuse or of drug overdose. The mean duration of substance abuse was 23 years, which, given the mean age of the subjects being 41 years, means that these patients have been abusing drugs most of their adult lives. Around 50% of patients have had an abstinence period from drug abuse of 6 months. 22 patients have denied concurrent illicit drug abuse. The most common reason given for subject relapse was family or relationship problems (30%), others being unemployment, social pressure and stress. Patients have admitted spending on average of 100-200 Euros per month purchasing illicit drugs. Furthermore, majority of patients have reported to have been experiencing current financial difficulties.

The following table demonstrates the co-use of alcohol and illicit drugs in the studied patient group. As shown below, a large number of the patients surveyed did not admit

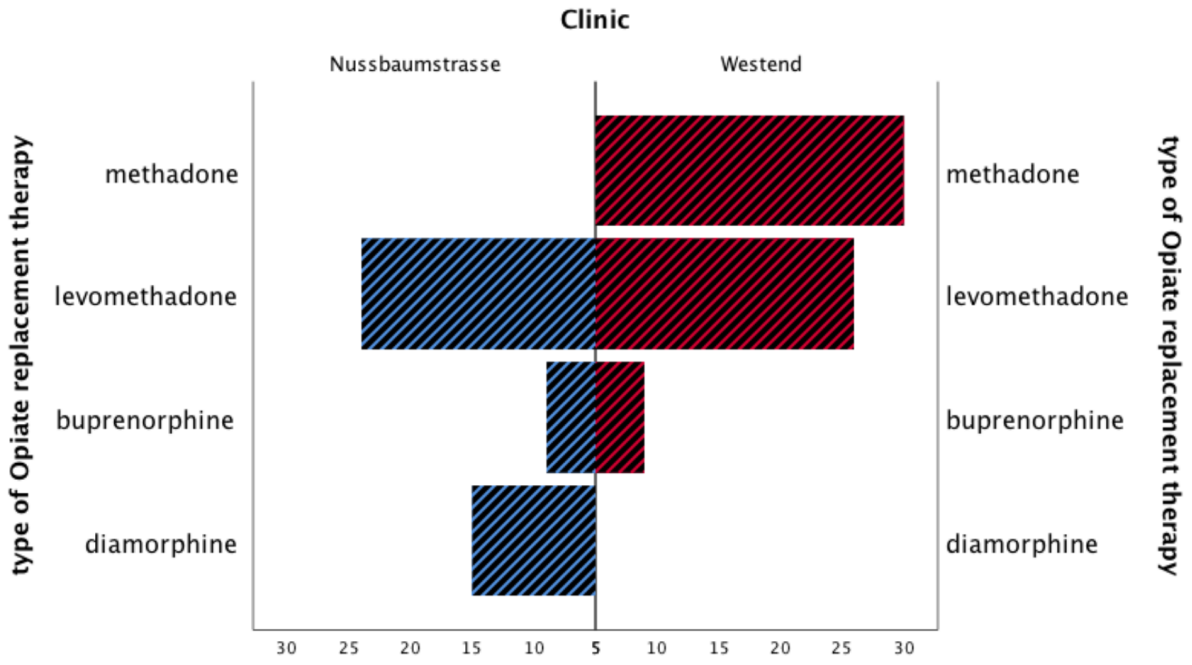

Abbildung 3.1: Demographic of patients on opiate substitution therapies in WSP and NBC taken in September 2015

to using illicit substances. Many of those who reported illicit drug use did not specify the amount, route nor the frequency of use. During the interviews, some patients were clearly hesitant to answer this question due to the possible implications, despite the reassurance of their confidentiality prior to conducting the surveys. Moreover, when stating the quantities of illicit drug consumption, most patients were very vague and gave large range of quantities taken. For example, drinking 10 to 15 beers a day, smoking a 'joint' once a day, or taking lorazepam from time to time once a week. Some patients had high and questionable amount of drug consumption, for example, 20g of Badesalz IV a day, which significantly increased the mean consumptions among all patients. Therefore, it should be noted that the estimated amounts of the illicit drug consumption could be inaccurate with a presumably large bias.

3.1.3 Benzodiazepine usage

Table 3.2 summarizes the pattern of benzodiazepine use in correlation to genders, BDI-II, PSQ scores; its usage in patients with diagnosis of depression, anxiety and chronic pain, as well as, comparing the dosage of benzodiazepine usage in those with and without concurrent use of antidepressants. It has been shown that males have a higher mean intake of benzodiazepines compared to females, but almost 80% of all female users have obtained

	Number of users	% in patient group	% of patients did not report usage	Average consumption per week in grams	Male	Female	Mean co-consumption of diazepam in mg per week
Alcohol	49	43	33	393	32	17	118
Cannabis	46	41	29	4.2	31	15	110
Cocaine	3	3	54	--	2	1	--
Heroin	30	26	50	4.8	24	6	160
Fentanyl	5	4	62	--	3	2	187
Amphetamines	4	3	52	--	2	2	93
Pregabalin	26	23	46	2.8	19	7	204
Badesalz	9	8	57	40	5	4	73

Tabelle 3.1: co- use of alcohol and illicit drugs with their mean consumption of benzodiazepine in mg of diazepam per week (n=113, male= 79, female=34)

it illegally. Of the 53 patients who have tested positive for benzodiazepine usage in random urine tests in the last 4 weeks of the study, only 39 patients have reported the source, type and dosage of their benzodiazepine usage.

As mentioned previously, benzodiazepine consumption was divided into 3 sub- groups, those being legal, such as from prescription by health professionals, illegally obtained on the black-market and those who used both sources. The mean amount of combined benzodiazepine usage among all 3 groups in converted diazepam in milligrams per week is 191, with the mean legal and illegal consumptions being 156mg and 163mg respectively.

One of the difficulties of the study, as mentioned before, is that we solely rely on the information that the patient discloses about the source and amount of illicit drug usage. If benzodiazepine has been prescribed by a health professional, it is at most times problematic to track when it was first given, the initial indication, the duration of usage and the initial dosage prescribed. It is also difficult to find and follow the source of subsequent prescriptions. Therefore, it is important to communicate with the clinicians who have prescribed the benzodiazepine after the patient has been discharged from their care, being either inpatient or ongoing outpatient care, to discuss the ongoing indication and duration of supposed usage to prevent forming addiction and drug trafficking.

	Legal source	Illegal source	Both	Total	Non-Benzodiazepine users	Mean diazepam in mg per week (in users)
Male	8	23	6	37	34	209
Female	2	13	1	16	18	107
Number reported	10	36	7	53	59	176
Number reported with dosage	10	24	5	39	_	191
Diazepam in mg per week	156	163	320	191	_	_
Diagnosed depression	9	26	6	41	21	196
Diagnosed anxiety	5	21	3	29	16	216
Chronic Pain	4	12	2	18	12	190
With antidepressant therapies	7	17	3	27	16	155
Without antidepressant therapies	3	16	3	22	30	242
Mean BDI scores	26	19	26	21	17	_
Mean PSQ scores	10	12	14	12	9	_

Tabelle 3.2: baseline characteristics of the use of benzodiazepine converted in mg of diazepam per week usage and its presumed sources (n=113, male= 79, female=34)

3.1.4 Nicotine dependence

Nicotine dependence was moderately high among the patients, with an average Fragerstrom score of 6. The mean years of nicotine dependence was 26 years. 36% of patients have attempted quitting, of which, 55% used complete abstinence, also known as the “cold turkey” method, whilst others, around 40% used nicotine replacement therapies. However, all of the patients who attempted quitting have relapsed after a mean period of 2.4 months,

due to reasons such as unemployment, stress and relationship troubles. It should be noted that we did not find any statistically significant between Fragerstrom scores against BDI-II, PSQ and benzodiazepine consumption in this study.

3.1.5 Depression profile

Based on the medical records, around 64 surveyed patients have known diagnosis of major depression and of these, 40 patients suffer from both depression and anxiety. From those around 30% of the patients have had previous suicide attempts and 26% have positive family history of depression. Only 21% of the patients receive ongoing therapies in the form of regular follow up through a psychiatrist and 39% are taking antidepressants either through a psychiatrist or illegally.

	Male	Female	SSRI	AAP	TCA	AAD	>1 antidepressant	Ongoing psychotherapy
Total number of patients	79	34	6	5	2	11	10	37
Depression	15	7	2	1	1	4	0	9
Depression and anxiety	24	16	4	1	1	3	8	27
Anxiety	6	2	0	1	0	0	1	1
Schizophrenia	1	2	0	1	0	1	0	2
Borderline personality	7	7	1	0	1	3	3	11
Bipolar disorder	4	4	1	1	1	2	1	5
Suicide attempts	13	8	2	1	1	3	4	14

Tabelle 3.3: categories of antidepressants use and ongoing psychotherapy in patients with diagnosed psychiatric illnesses (n=113, male= 79, female=34)

Antidepressants

For the purpose of the study, we have divided the antidepressants taken by the patients into 5 categories. Those being serotonin reuptake inhibitors (SSRIs), atypical antipsychotics (AAPs), tricyclic antidepressants (TCAs), atypical antidepressant (AAD) and those who use more than one type of antidepressant. As shown in table 3.3 and in the diagram

below, the highest percentage of patients with psychiatric illnesses takes an atypical antidepressant, followed by patients with more than one antidepressant. The least number of patients use an TCA, possibly due to its unwanted side-effect profile and also due to the risk of long-QT syndrome in combination with methadone therapy.

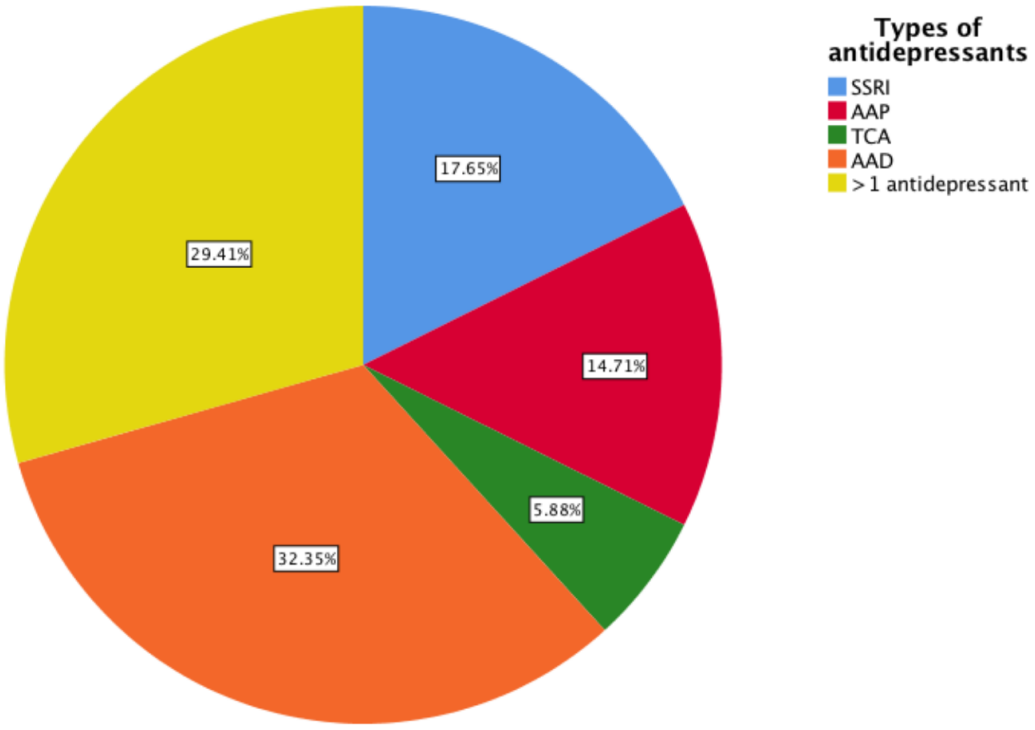

Abbildung 3.2: percentage of patients with different catagories of psychiatric medications. (n=34)

3.1.6 Social Structure

Around half of the patients have finished Hauptschule and about a quarter finished Realschule. The majority of patients went on to complete an apprenticeship in diverse fields, such as in mechanics, handiworks, construction, administration and health care. However, around 63% of patients are currently unemployed, of which around 50% have not worked for longer than 12 months. 70% admit to being on social benefits. The vast majority (82%) of the 38 subjects who are currently employed stated that they are satisfied with their jobs and only a few works in jobs with shifts.

Most of the patients (69%) live in rental apartments, followed by those living in Pension (16%). A small fraction (6%) are self-reported as homeless. In terms of relationship status, 78% of patients are reported to be currently living alone, either single, separated

or windowed. Around 30% of subjects have children and stated to be satisfied with their current family life.

3.1.7 Chronic Co-morbidities

Chronic pain

For the purpose of this study, we documented some of the somatic co-morbidities that can contribute to insomnia and depression. Around 28% of patients suffer from chronic pain. Although whether someone considers themselves as suffering from pain is a very subjective question, in the subjects studied, pain can originate in particular from chronic ulcers, abscesses and infections from injection sites, poor wound care, polyneuropathy from vitamin deficiencies in chronic alcohol abuse and poor diet, just to name a few. Moreover, this patient group also tends to have a higher rate of accidents and injuries. From my own clinical experience working in the emergency room, they are notably more susceptible to burns injuries due to the often, somnolent state after drug consumption compared to the general population.

	Male	Female	Total % in the group	Mean PSQ scores	Mean BDI-II scores	Mean Fragerstrom scores	Mean diazepam use in mg per week	Mean pregabalin use in mg per week
COPD	14	4	15	11	21	6.3	75	3525
Asthma	7	2	7	13	22	6.5	117	4200
Hepatitis C	43	22	57	11	20	6.2	106	3215
Chronic pain	22	10	28	12	22	5.4	190	2625
Peripheral polyneuropathy	5	2	6	13	24	6	61	-
Restless leg syndrome	3	2	4	12	21	5.2	70	4200
Sleep apnea	7	4	10	15	23	5.9	131	2100
Gastric reflux	7	6	11	11	22	7	47	2625

Tabelle 3.4: somatic co-morbidities and their correlations to PSQ, BDI-II, Fragerstrom scores, diazepam and pregabalin usages in mg per week (n=113)

Chronic respiratory insufficiency

Chronic respiratory insufficiency, such as COPD due to smoking leads to nocturnal coughing, shortness of breath, recurrent respiratory tract infections, right sided heart failure and overall decreased quality of life. One would have thought this might very well be a contributor to depression and insomnia. As seen in table 3.4, only 15% of the surveyed patients reported to have diagnosed COPD and 7% have asthma. Only some of patients with either diagnosis have been adequately treated with the appropriate medications. As mentioned previously, the studied group had an overall mean Fragerstrom score of 6.2 indicating moderately- high nicotine dependence. Interestingly, the mean Fragerstrom scores in patients with COPD and asthma are 6.3 and 6.5 respectively. The differences between the Fragerstrom scores of those with and without chronic respiratory illnesses are minimal, thus, lacking statistical significance between the two groups. Moreover, no significance has been found between their PSQ and BDI-II scores in this study. Most patients in this group possibly have COPD in different degrees of severity but most have not had the proper diagnosis or have not adhered to the treatments, resulting in the inconclusive results.

Sleep Apnea

Patients with sleep apnea only make up 10% of all patients in the study. The survey only asked if there has been a positive diagnosis from a respiratory physician, but did not specify whether they are undergoing concurrent therapies, such as, the use of nocturnal C- PAP machines and whether this condition has impacted on the quality of their sleep. As shown in table 3.4, these patients have a higher PSQ score of 15 and BDI-II score of 23 compared to the mean of 12 and 21 respectively among all patients. Thus, we can conclude that there is some tentative evidence that sleep apnea is positively correlated to insomnia and depression among ORT patients but due to the small number of patients with sleep apnea in this study no statistical relevance has been found.

Hepatitis C

Around 57% of patients from both clinics have reported to have or have had hepatitis C infection. Of which however, only 13% of the patients have reported to have currently inactive infections. Despite routine assessments of HCV viral loads, 6- monthly abdominal ultrasound follow-ups and referrals for therapies to Hepatologists, almost 50% of infected patients from both clinics shown in the following graph in the study claimed to have not received any treatment. Hepatitis C positive patients from NBC have a much higher rate of treatment compared with WSP, being 72% and 36% respectively. As mentioned in introduction section 5.1, new oral direct acting antiviral (DAA) treatments for HCV have been available in Germany since 2015. The treatments are shorter in duration, better tolerated and are associated with higher average cure rates. As of the time of this study, 38% of the patients have received interferon therapy, but only 12% of patients in total from both clinics have received DAA treatment. Many patients from WSP claimed during the surveys that they would like to participate in the DAA treatment. They claimed they

have either not been adequately informed or assessed, do not fit the treatment criterion and some have been denied the therapy due to their lack of treatment compliance.

3.2 Data analysis

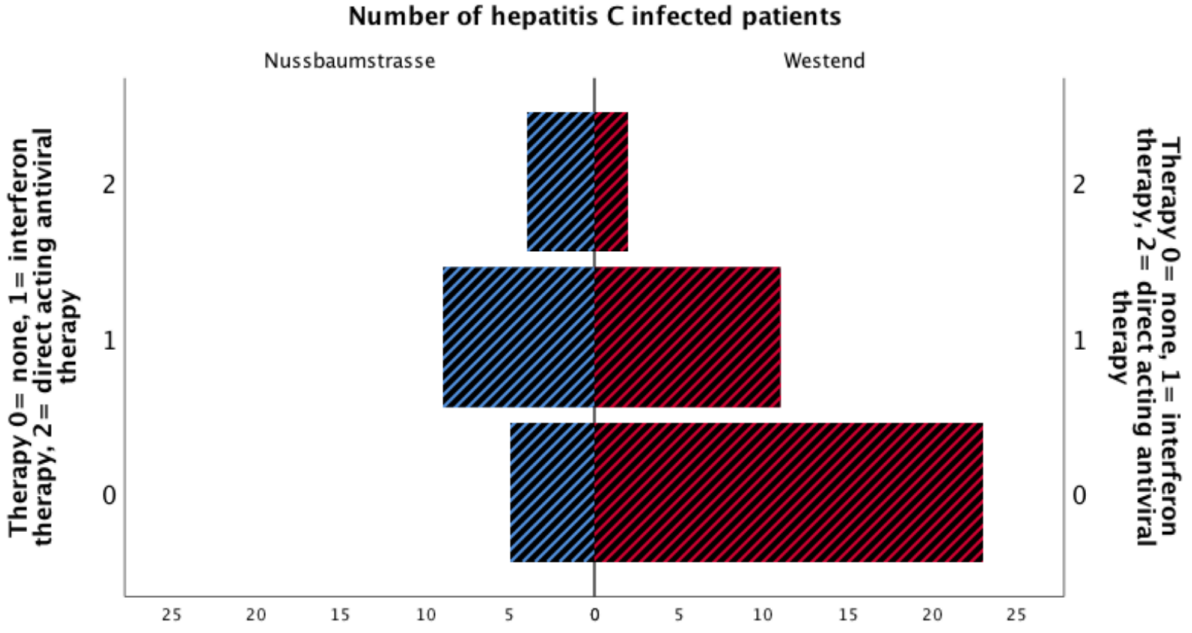

Abbildung 3.3: treatment distribution in hepatitis C infected patients (n=65).

3.2.1 Effect of ORT on insomnia and depression

The mean BDI-II score among all patients is 19.4 and comparatively 26 in patients receiving levomethadone. By further comparing ORT from both clinics BDI -II Scores using the One-way Anova, we have found that patients who have been receiving levomethadone therapy have the highest mean score of BDI-II. In the post- hoc analysis, BDI-II scores are lowest in patients who are substituted with buprenorphine compared to with levomethadone to the significance of 0.01. BDI score did not significantly alter with the dose of levomethadone.

Using the same method, we have measured the mean PSQ scores among the different ORT groups. The mean PSQ score across all groups was 10.5. Patients who have been treated on diamorphine on the other hand are found to have a lower PSQ score on average,

especially compared with patients on levomethadone. PSQ score did not change significantly with levomethadone dose. The results are nonetheless not significantly different possibly due to the small sample size of diamorphine patients. It should be noted that out of the 15 diamorphine patients who participated in the study, only 7 have completed the full PSQ survey and the results of which were used for the calculations. Incomplete surveys of both BDI-II and PSQ were discarded for calculation purposes.

It is interesting also to note, that 49% of the surveyed patients have admitted to subjectively improving their sleeping difficulties after commencing ORT, as ORT decreases the withdrawal symptoms from opiate abuse especially at night due to the long half-lives of ORT compared to opiates. 38% stated that sleep quality has remained the same and for 14 patients it has worsened, with a few complaining of the drowsy effect of methadone during the day. Once again it is important to note that this was a subjective evaluation as no PSQ scores were obtained prior to commencing ORT to compare the results.

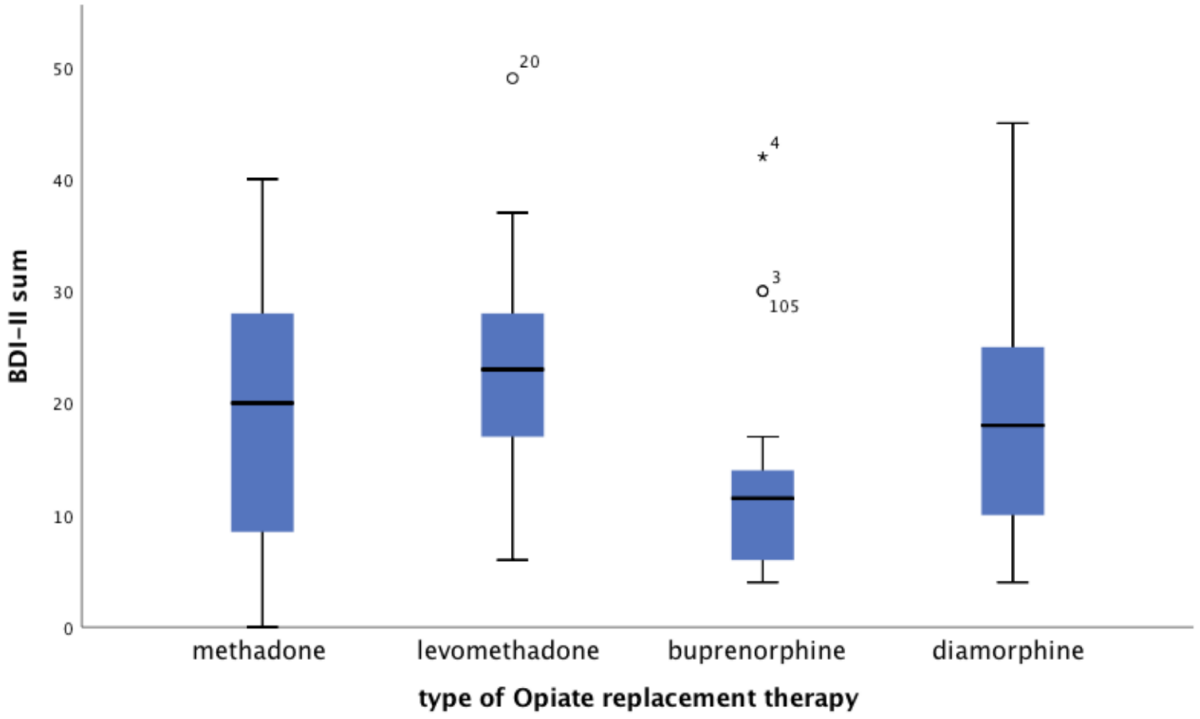

Abbildung 3.4: BDI scores in each patient group of ORTS (n=113)

3.3 Benzodiazepine abuse

One of the focuses of this thesis is to explore the nature of the relationship between insomnia and abuse of benzodiazepines. As mentioned previously, the use of benzodiazepines is

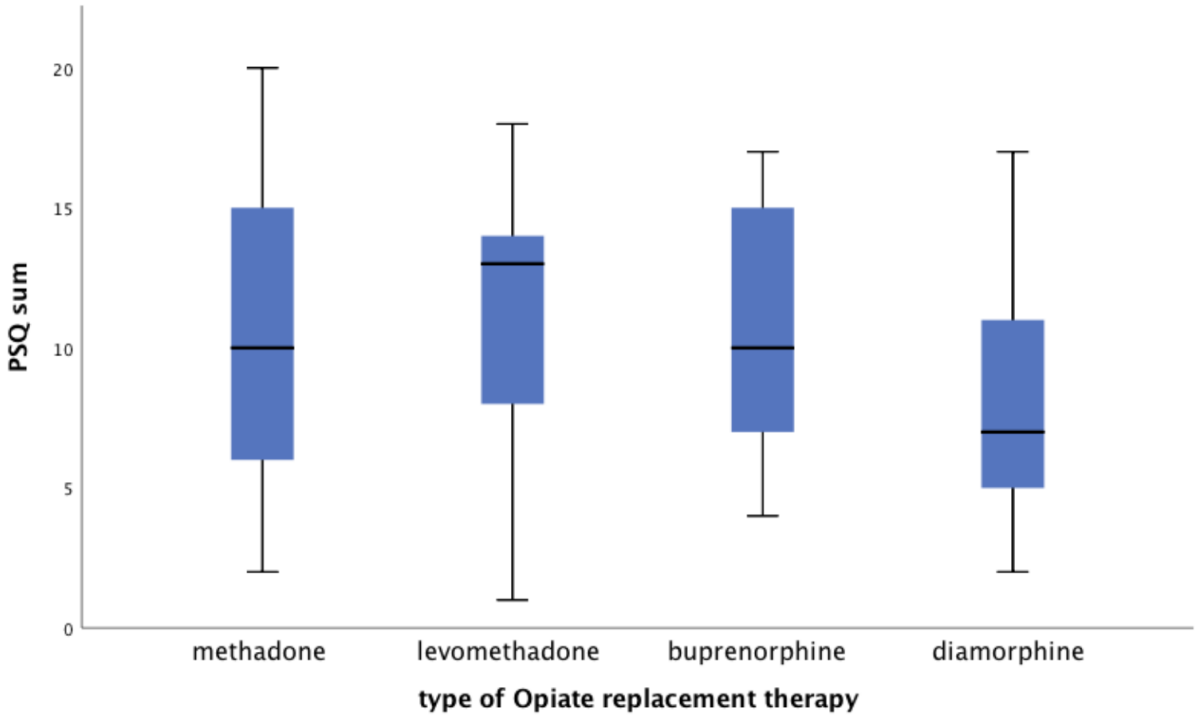

Abbildung 3.5: PSQ scores in each patients group of ORT (n=113)

particularly dangerous in this group of patients in combination with opiate abuse, as it leads to an increased risk of respiratory depression. Concurrent use of benzodiazepines, opiates and methadone has been implicated in methadone related deaths, as benzodiazepines are likely to compete with methadone and opiate for opiate receptors and may in addition inhibit the degradation of methadone in the liver [20, 30]. As shown in table 3.1, patients who abuse opiates, such as heroin and fentanyl, tend to have a higher mean usage of benzodiazepine compared to the co-use with other illicit substances. The highest usage was together with pregabalin. It should be noted that for the purpose of calculations, we have converted the different types of benzodiazepines reported into a mean dose of milligrams of diazepam used per week. Most patients consumed a mixture of different benzodiazepines and different routes of consumption were reported being oral, nasal and IV.

Using linear regression in figure 3.6, we are able to prove that the mean amount of benzodiazepine used converted in milligrams of diazepam is positively correlated to PSQ scores. The mean PSQ score in benzodiazepine users is 12, compared to 9 in non- users. Most patients use less than 200mg of benzodiazepine. The highest PSQ scores are correlated to the mean use of 400mg of diazepam per week. From this we can conclude that the amount of benzodiazepine usage increases with severity of insomnia. As shown in table 3.2, there's also tentative evidence that illegal benzodiazepine users have higher PSQ scores in spite of

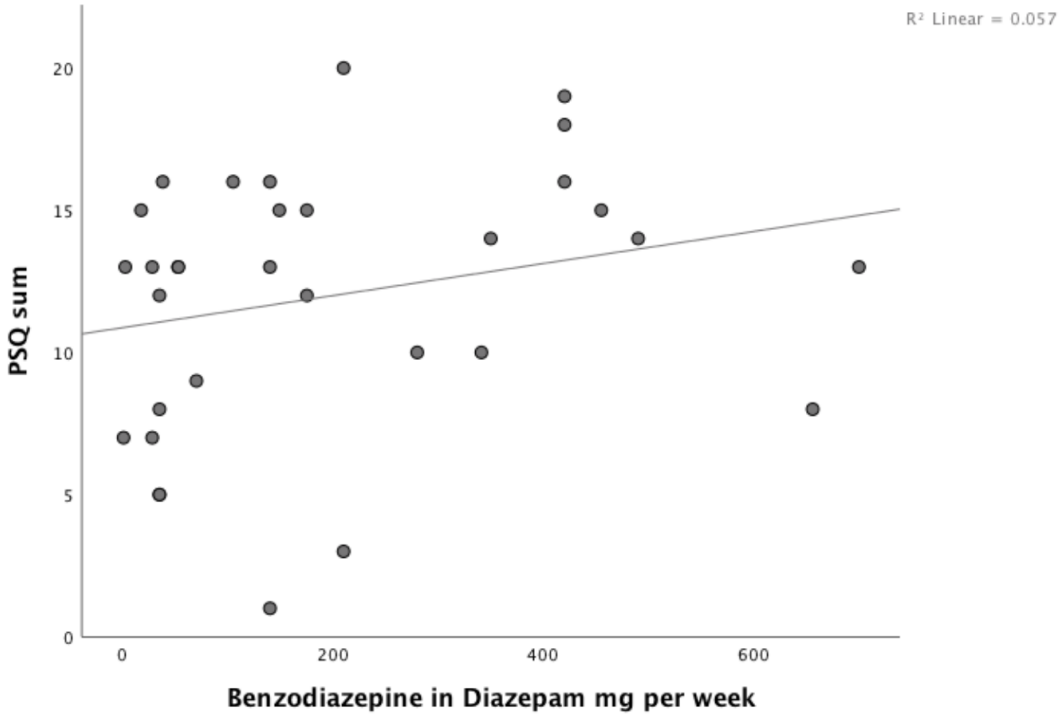

Abbildung 3.6: correlation between the dose of benzodiazepine usage in self- reported users and those with positive urine benzodiazepine analysis and PSQ score (n= 53)

the fact that the amount of benzodiazepine used between the sub- groups is not significant.

Using the independent sample T test, we found that patients with a higher BDI-II score and who are taking benzodiazepines are significantly correlated to having diagnosed depression, anxiety and bipolar disorders, borderline personality and previous suicide attempts. The following bar graph demonstrates that patients with both anxiety disorder and depression consumes the highest mean average of benzodiazepines compared to patients with only depression; and to patients with no known depression and anxiety disorders. It is also interesting to note, that from the studied patient group, the 8 patients with single diagnosis of anxiety did not report taking benzodiazepines.

Furthermore, in patients with a known diagnosis of depression, BDI –II scores do not statistically relate to the presence of on-going psychotherapies. That is, patients who are currently being treated with forms of ambulant psychotherapies from a psychiatrist do not have significantly improved BDI-II scores compared to those who do not. It was not specified in the questionnaire the type of psychotherapy nor the duration or the frequency of treatment. This could also relate to the non-compliancy of patients to therapy as ambulant psychotherapies are in most cases voluntary.

Our analysis has on the other hand shown that, those with diagnosed depression and an-

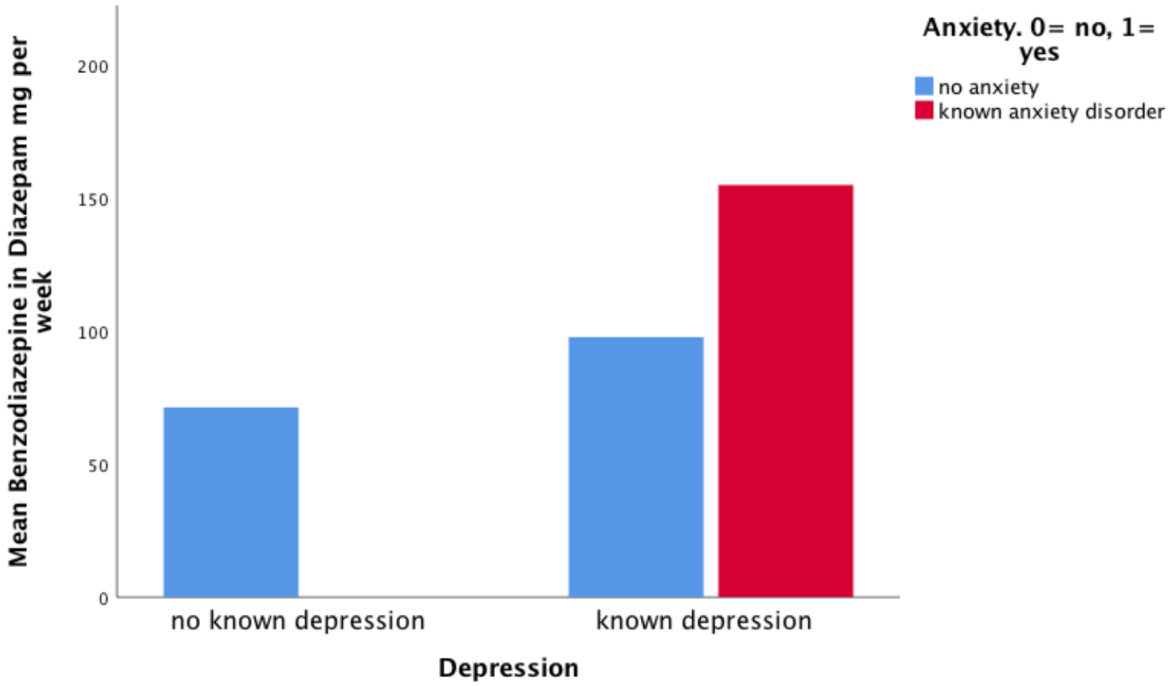

Abbildung 3.7: characteristics of benzodiazepine usage in patients with anxiety and/or depression disorders. (with only anxiety disorder n= 8, with only diagnosed depression n= 22, with both n=40)

xiety disorders who are being treated with antidepressants, are likely to use a lower dosage of benzodiazepines compare to those who are not receiving medications. We could not statistically deduce from this data set the specific group of antidepressants that corresponded to the least amount of benzodiazepine usage.

3.4 Effect of sub-variables on depression and insomnia

In this study, we chose 5 sub-variables, which can potentially impact on sleep and depression in these patients, those being, gender, BMI, unemployment, self- reported chronic pain and undesirable living arrangements. The last co-variant should also be noted as subjective, and this was purely based on the patients' perspective of whether they are satisfied with their current living arrangements and if this state of living has impacted on their quality of sleep. BMI and gender had no significant relationships to the tested variables.

We calculated each of the sub- variables against BDI- II and PSQ scores using the independent T- test and found that patients with reported chronic pain syndrome have been found to have significantly higher BDI-II scores compared to those without pain. As

Abbildung 3.8: Comparing benzodiazepine usage in patients with diagnosis of depression and anxiety disorder who are currently on antidepressant medications and those who are not (anxiety disorders on antidepressants n=2, not on antidepressants n= 6; diagnosed depression on antidepressants n=8, not on antidepressants n= 14; both anxiety and depression disorders on antidepressants n=17, not on antidepressants n=23)

seen in table 3.4, patients who suffer from chronic pain also consume the highest amount of benzodiazepine compared to patients who suffer from other co-morbidities, with 12 out of 18 patients obtaining it illegally (table 3.2).

PSQ scores on the other hand, were surprisingly not correlated to the undesirable living arrangements, but to unemployment as shown in figure 3.10. As mentioned in the previous section, half of the patients who are currently unemployed are on social benefits and have not worked for longer than 12 months. In the interview, subjects often commented in the questionnaire on their high financial burden and the lack of occupational engagement during the day would lead to their insomnia.

As mentioned previously, the majority of patients live alone and in rental apartments. Only a small number of patients are reported as homeless but most of which are temporarily staying with friends until they find housing. Patients who are living in Pensions reported that they often would have to share a room with another person also suffering from addiction and/or psychiatric illnesses. One would expect these circumstances would

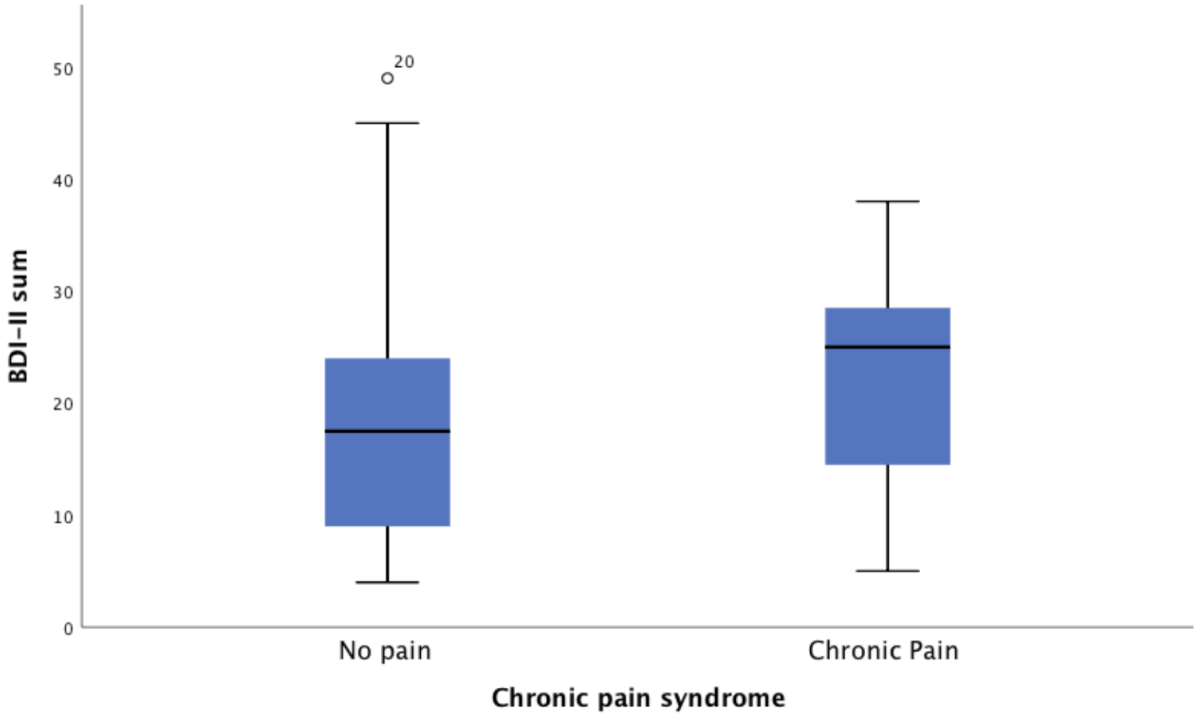

Abbildung 3.9: Comparison of BDI-II scores in patients with and without self- reported chronic pain syndrome (n= 113)

have a negatively impact on the sleep quality. Surprisingly no statistical relevance was found.

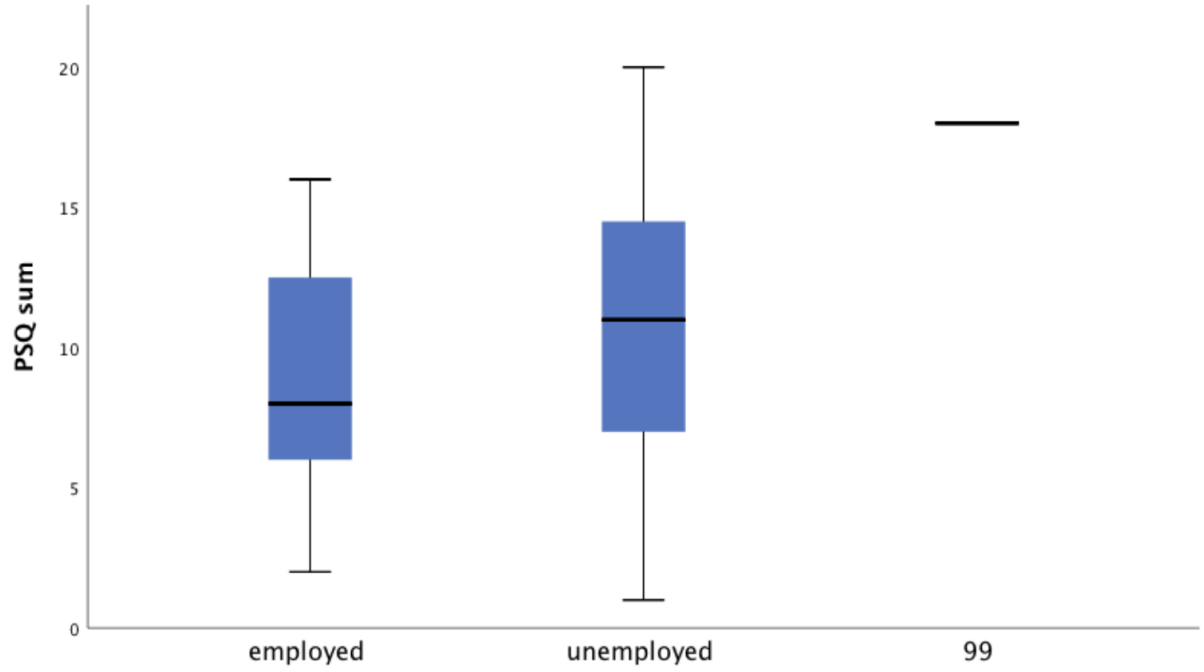

Abbildung 3.10: Comparison of PSQ scores in currently employed and unemployed patients. (n=113, 99 = missing responses)

Kapitel 4

Discussion

In this study, we explored four main areas of on-going concerns in the treatment of opiate addiction: insomnia, depression, benzodiazepine abuse and chronic pain. As we have discovered throughout the study, not only do these factors assert influences on one another, there are also interactions of ORT and substance abuse with each of these studied areas. In the following section, we will further explore each of the areas of the study and, in doing so, also compare our results with those from publications worldwide.

4.1 Summary of the results of the study

1. There are a multitude of factors causing insomnia in opiate addicted patients. ORT has shown in this study to have led to an overall improvement in sleep quality.

2. Levomethadone therapy in the studied patients has been associated with higher rates of depression and possibly insomnia compared to other forms of ORT. This effect had been found independent of the dose of levomethadone. Buprenorphine has been linked to lower concurrence of depression and diamorphine has been tentatively associated with better sleep qualities.

3. The use of benzodiazepines is positively correlated with depression and anxiety disorders. The dosage of benzodiazepines used is negatively correlated to the usage of antidepressants, of which mirtazapine is the most commonly prescribed in this group of patients. It can be concluded that patients who are effectively medicated for their depressive and/or anxiety disorders are likely to use a lower dosage of benzodiazepines compare to those who are not receiving medications. On the other hand, the reduction of the use of benzodiazepines could also be attributed in this case to the effectivity of mirtazapine on increasing the quality of sleep and reducing the state of anxiety.

4. Benzodiazepines are more frequently used and also in higher dosages in insomniac patients. This was either prescribed or acquired illegally for treating sleep disorders. Patients with the highest PSQ scores use a combination from both sources.

5. Chronic pain syndrome is strongly associated with patients suffering from depression. Patients with chronic pain syndromes are also likely to illegally abuse benzodiazepines.

6. From the somatic chronic co-morbidities surveyed, insomnia is only positively correlated to sleep apnoea in a small group of patients. The severity of insomnia is also not related to the type of accommodation the patient has but to their current employment status.

4.2 Insomnia

Chronic sleep disturbance is one of the biggest areas of concern in addiction medicine. All patients in this study suffer from various degrees of insomnia, with an average PSQ score of 12 in benzodiazepine users and 9 in non-users. Both groups have significantly higher PSQ scores than the international cut-off score of 5 to classify patients with insomnia and 10 for those with severe insomnia. The reasons attributed to insomnia are highly complex among ORT patients, and it has mainly been identified as iatrogenic, due to side effects of medications; the result of substance abuse, with the incidence being 75% in ORT population [38]; in association with the triad of chronic pain and depression; and finally due to psychiatric illnesses and social circumstances. Thus, referral for sleep medicine should generally be given to all ORT patients.

4.2.1 Iatrogenic

As mentioned previously in this thesis, the use of opiates has been known to be a contributor to insomnia by causing circadian rhythm abnormalities as well as contributing to the development of central sleep apnoea [40]. Patients could also suffer from its side effects such as bladder dysfunction, pruritus and constipation, all of which would affect their sleep quality [78]. Figure 3.5 showed the highest PSQ scores to be in ORT patients substituted with levomethadone, especially compared to those being treated with diamorphine. It is unclear why patients treated with levomethadone have a worse PSQ score compared to those on methadone in our study, as it should have less side effects compared to methadone [15]. Iserhagen and Struck performed a study evaluating PSQ scores in ORT patients in 34 ORT clinics across Germany and found that patients substituted with levomethadone have significantly higher PSQ scores compared to those using buprenorphine. It should be noted diamorphine was not part of that study as it was introduced in Germany after the study period. The negative effect of levomethadone on sleep was particularly evident in both the ability to sleep throughout the night (Durchschlafstörung) and the effects of nocturnal micturition (nächtliches Wasserlassen) [79]. In the case of “Durchschlafstörung”, it could also be related to the direct relationship between methadone/levomethadone and sleep apnoea [78], as well as its increase in the time spent in light-sleep and subsequent decrease in the deep-sleep period [80]. Buprenorphine has a longer half-life compared to

methadone, and its associated less nocturnal withdrawal symptoms could lead to better sleep qualities.

Iserhagen and Struck also found positive correlation between PSQ scores and the dosage of all ORTs in the study. This could either be due to the cumulative side effects of the ORT or to the fact that patients who require a higher dose of ORT tend to be more physically and psychiatrically ill and thus also tend to suffer from sleeping disturbances [79]. In our study, we found both BDI-II and PSQ scores did not appear to significantly change with the dose of levomethadone.

As of writing this thesis, no literature can be found which looks at the effect of diamorphine on insomnia, likely because it is still a relatively new ORT in Germany. This could an interesting area of research, as it has shown even among a small group of diamorphine patients in this study to tentatively improve the severity of sleep disturbance.

Despite the side effects of ORT mentioned above, around half of the patients in the study reported subjective improvement in their sleep after commencing ORT.

4.2.2 Substance-induced insomnia

Substance-induced insomnia can be due to the use of ORT and/or as a result of alcohol and illicit drug abuse. It is difficult or almost impossible to isolate the main substance causing insomnia in ORT patients due to their complex substance abuse profiles. Almost all substances can lead to sleep disturbance. Around 40% of the ORT patients in the study reported drinking a significant amount of alcohol per week, with a mean consumption of 56g per day, which is well over the recommended daily limit. Alcohol is known to disrupt circadian rhythms, as well as interfere with upper airway musculature leading to peripheral sleep apnoea [38]. Iserhagen and Stuck also found in their study a negative effect of alcohol in PSQ scores [79]. Cannabis also showed a disturbance in the sleep cycle and withdrawal symptoms causing vivid dreams [38]. The main cause of substance-induced insomnia in the studied group is opiates, as both ORT and illicit opiates not only lead to disruption in circadian rhythms and functional impairment of respiratory muscles but also suppression of central respiratory drive leading to central sleep apnoea [40]. Pregabalin on the other hand, has been shown to improve sleep quality especially in patients suffering from pain syndromes [81]. But more studies are needed to see the long-term effects of pregabalin usage on the sleep cycle in ORT patients.

4.2.3 Social factors

Another major challenge to working with ORT patients is the management of their complex social situations. In this study, the focus was on unemployment and undesirable living arrangement as potential sub-variables, which may affect the subjects' mood and quality of sleep. Only a fraction of patients in WPS during the interview reported living in sub-optimal living conditions normally either sharing their room with another person, often an addict, or in crammed conditions where it is loud with little privacy. We asked the patients if they were satisfied with their sleeping arrangements and used their answers as either 'yes'

or 'no' in the calculation rather than statistically correlating each type of accommodation with the PSQ scores. No correlation between their satisfaction in their current sleeping arrangement and PSQ scores were found.

Figure 3.10 shows a significant difference in the PSQ scores between employed and unemployed subjects. Despite regular assistance helping patients with finding employment from the social workers in both practices, more than 60% of the patients were unemployed, half of which have been for longer than one year. Many of them were also reported to be non-compliant with "One Euro Jobs". It is understandably difficult for ORT patients to find stable long-term employment. The majority of patients have criminal record on top of their long history of drug usage, psychiatric and medical illnesses, as well as being incompliant to attend work regularly making them unattractive candidates for employers. Having a regular job would help ORT patients to establish a daily routine and regular sleep pattern. Most of the employed subjects in WSP worked in jobs involving physical labor. During the interview, many of them stated that physical exhaustion from working also helps to initiate their sleep and kept them abstinent from substance abuse.

4.3 Depression

Out of the 113 patients in the study, around 50% suffered from known depression, and the majority of which suffered from combined anxiety disorders. It is clinically difficult to distinguish the two disorders, as the symptoms often manifest in an overlapping manner. This is particularly challenging when substance abuse and complex co-morbidities are involved. The mean BDI-II among all patients was 19.4, which fell within the international BDI-II score for having mild depression [72]. As mentioned previously, a higher cut off of the BDI-II score for ORT patients normally apply due to the effect of the somatic symptoms, such as chronic pain on the scores, which can often overlap with symptoms of depression [69],[73],[71]. We will discuss in the following sections how ORT could possibly affect the BDI-II scores, the use and effectivity of different classes of antidepressants, and the use of psychotherapies.

4.3.1 Effect of ORT on depression

Studies have shown that ORT improves the mood in opiate addicted patients with manifestation of depressive symptoms dropping by 31% 6 months after initiating therapy. This was due to a combination of reducing illicit drug usage, and it also involves support from psychiatrists, psychotherapist and social workers [46, 82, 83]. Depression has also been suggested as an "internal cue" for triggering drug craving, thus, improvement in the state of mood also helps in preventing substance abuse relapses.

Methadone therapy alone has shown little antidepressant effect and it can cause mood swings and might worsen depressive symptoms in the initial phase of therapy [83, 84]. Kosten et. al. found that the depression scales in patients using buprenorphine in ORT improved by 63% over the first month after initiating therapy [84]. Buprenorphine is a long-

acting partial agonist at the -receptor, but also acts as an antagonist at the kappa receptor. Agonist effects on the k-receptor is associated with dysphoric effects, hence antagonist effects help to reduce responses to negative emotional stimuli in patients with depression or anxiety [85, 86]. This suggests that buprenorphine might be an effective ORT used in patients with mood disorders. We have also seen in our study, shown in figure 3.4, that patients treated with buprenorphine have had comparably lower BDI-II score compared to other ORTs, especially compared with levomethadone.

4.3.2 Antidepressant therapies

Figure 3.3 illustrated that atypical antidepressant was the most common group of antidepressants taken by patients, but many were taking more than one antidepressant, followed by an SSRI. The most common atypical antidepressant prescribed in this study was mirtazapine. It mainly acts by increasing the level of monoamine neurotransmitters, specifically serotonin and norepinephrine, but it also has anxiolytic and sedative effects, thus, also effective in reducing symptoms of anxiety and improving the quality of sleep. In Germany, mirtazapine has often been prescribed in low dosages by general practitioners, starting with dosages of typically 7.5mg in the evening as off-label usage for patients suffering with insomnia. From experience, we have found this usage to be particularly effective in patients who have problems maintaining their sleep and in those who suffer concomitantly from anxiety disorders.

Both Nunes and Rounsaville [82, 83] showed that patients with substance-induced mood disorders, that is substance abuse either contributed to their affected symptoms or as a result of it, have shown both an improvement of their mood and reduction in substance abuse after using antidepressants compared to placebo. In our calculations, we did not correlate the use of antidepressants to the dosages of individual ORTs. From clinical contact with these patients, we had the impression that many of them were using narcotics to relieve their symptoms of anxiety and depression. This could manifest in using higher doses of ORT. It would be interesting to see if the use of antidepressants would also in turn lower the dosages of ORT patients require. Since there are many dynamic factors which can affect patients' mood, such as their current social situations and acute illnesses, a longitudinal study would be more appropriate to answer this question.

4.3.3 Psychotherapies

Patients from WPS with psychiatric disorders were mainly referred to an outpatient psychiatrist to undergo regular follow-ups and psychotherapies. Patients from NBC tend to be in a worse state of psychiatric health and were treated in part by in-hospital psychiatrists. We did not further investigate the frequency, duration nor types of psychotherapies patients were receiving. Table 3.3 shows that 67% patients with diagnosed depression and anxiety underwent psychotherapies, but BDI-II scores did not significantly differ between those who received psychotherapy and those who did not. This could be due to a variety

of factors and, due to the lack of information obtained in this study, no conclusions can be made.

4.4 Use of Benzodiazepines

As discussed extensively throughout this thesis, the abuse of benzodiazepines is particularly concerning in ORT patients due to the accumulative effect on respiratory suppression. Benzodiazepines have been identified in 50 to 80% of heroin-related deaths in Germany, Ireland and UK [31]. For unclear reasons, the frequency of benzodiazepine misuse has also been reported to increase with the length of ORT treatment [25]. As shown in table 3.2, a total of 53 patients have been tested positive for benzodiazepine usage, 37 being males and 16 females, which amounts to roughly 47% of patients in each gender group. The total number of users (regardless of gender) was also 47% of the total patient numbers, which fell within the average of 30-50% of opiate addicted patients cited illegally abusing benzodiazepine in registered ORT programs Europe-wide [25]. The average amount of benzodiazepine consumed per week was 191mg of diazepam. Male subjects reported a much higher intake of benzodiazepines, being 209mg, compared to 107mg used by female subjects. The number of patients with illegal sources of benzodiazepine intake is more than 3 times higher than those with legal sources and a small number reported to taking both.

As seen in table 3.1, heroin and fentanyl users have higher means of consumptions of benzodiazepine compared to the co-use of other illicit drugs. In the study, many patients in the WSP reported to crushing, mixing and injecting various strengths of benzodiazepine tablets with heroin. It was always thought by us that the patients wanted to do this due to the 'down' effects produced by benzodiazepine to oppose the 'highs' from opiates. However, literature also suggested that when injected, benzodiazepine can prolong the intensity and duration of opioid effects [25], as well as to combat the symptoms of opiate withdrawal.

It has also been found in the study that patients who were substituted with methadone have the highest mean benzodiazepine usage. This was not correlated to the dosage of methadone used. We did not further investigate this finding, as only a small fraction, being 26% of the studied patients with diverse psychiatric and physical co-morbidities were substituted with methadone, and this only included patients from WSP. Thus, it was hard to interpret the significance of this result.

4.4.1 Relationship between benzodiazepine, depression and anxiety

In this study, a higher percentage of females suffered from both depression and anxiety compared to males. As seen in figure 3.7, patients with both disorders abused more benzodiazepines compared to those with only depression. It is however interesting to note that, although female patients use much smaller amounts of benzodiazepine compared to the males, almost 80% of all female users have obtained it illegally. This was thought by us to

be related to the fact that female patients were using benzodiazepine to self-alleviate their anxiety symptoms.

In a study conducted in Toronto with patients with major depression disorder, it is found that more female patients, especially those with an associated panic disorder used benzodiazepines on a regular basis to alleviate their symptoms [51]. Although they used a different scoring system than we did to measure the severity of the state of depression, no differences in scores were found between the benzodiazepine user and non-user groups. However, significant differences in their functional status, and in certain symptoms such as anhedonia, were found [51]. This can either be due to the symptoms of depression or to the use of benzodiazepines. In our study, the BDI scores differ between benzodiazepine users and non-users, although not significantly. This suggests that the use of benzodiazepine does not directly reflect the severity of depression but it can be rather a predictor of a patients' functional status, which in our case correlated to the severity of their insomnia.

It has been found in some literature that patients with depression are likely to initiate benzodiazepine usage during antidepressant therapy, depending on the type of antidepressant given. This has been further complicated by the fact that anxiety disorder is common in patients with depression. Some published reports have claimed that more patients with depression who have been treated with SSRIs were more likely to have abused benzodiazepine compared to those treated with TCA due to less sedative effects of the SSRIs [51, 53, 87]. SSRIs might have to be supplemented with benzodiazepines more frequently to manage symptoms of anxiety and insomnia.

Perhaps due to the sedative effects of antidepressants, such as mirtazapine or TCA taken by our patients, or to the effective management of their symptoms, table 3.2 and the analysis illustrated in figure 3.8 both show that patients who have been pharmacologically treated for depression and anxiety disorder require significantly less amounts of benzodiazepine compared to those patients who were not medicated. Unfortunately, this patient sample was too small to explore which group of antidepressants was most correlated with the reduction of benzodiazepine usage.

4.4.2 Relationship between benzodiazepine and sleep

This study reports a significant positive correlation between PSQ scores and the amount of benzodiazepine used. This is demonstrated in the linear regression shown in figure 3.6. The study by Isernhagen, K., and Struck also showed that patients using benzodiazepines have the highest PSQ scores, followed by the use of antidepressants [79], which would correlate to the frequent use of mirtazapine to treat insomnia.

As mentioned throughout the thesis, it is difficult to track when and where benzodiazepines were initially prescribed and the length nor the indication of its usage. The cause of insomnia in ORT patients can vary vastly from patient to patient. Thus, it is conceivable that benzodiazepines are prescribed by physicians to ORT patients in order to aid in the short-term treatment of insomnia and, following the prescription period, patients have then sought illegal means of further self-medicate without addressing the underlying cause of their sleeping problems.

The major concern of benzodiazepine usage in opiate abuse is respiratory depression. Table 3.4 illustrates 10% of patients have diagnosed sleep apnoea with high PSQ scores. These patients were additionally abusing high amounts of benzodiazepines, to assist their insomnia, further increasing the risk of respiratory depression. Figure 3.6 demonstrates that the amount of benzodiazepine usage increases with severity of insomnia. Table 3.2 further shows that non-benzodiazepine users have a lower PSQ score compared to users, and users who used both legal and illegal sources have the highest PSQ scores. Patients who use illegal sources of benzodiazepine have slightly higher PSQ scores compared to those who claimed to have obtained it legally. For the reasons mentioned previously, the actual sources of benzodiazepines reported by patients are almost impossible to verify. It is also difficult to determine if these patients took benzodiazepine to initiate sleep or also for other purposes, such as for anxiolytic effects, heroin withdrawal etc. as these factors can also lead to insomnia. Furthermore, discontinuation of benzodiazepines can cause intense withdrawal symptoms most commonly resulting in sleep disturbance.

4.4.3 Relationship between benzodiazepine and pregabalin usage

Although we did not explore the use of pregabalin in ORT patients in this study, it was nevertheless interesting to point out that the highest mean usage of benzodiazepines were patients who were also using pregabalin. This made up roughly 23% of the studied patient group and the mean amount of diazepam used per week was almost twice as much as that used in conjunction with alcohol or cannabis. Pregabalin has been used for the treatment of neuropathic pain, epilepsy and off-label uses for the treatment of alcohol withdrawals, migraines, and in certain psychiatric illnesses for its anxiolytic effects [88],[89]. Perhaps due to the small sample size of patients in this study, there was no significance found with its usage in patients with chronic pain, and no patients with peripheral neuropathy were reported to use pregabalin. As seen in table 3.4, the highest mean dosages of pregabalin were documented in patients with restless leg syndrome. A Norwegian study in 2010 with around 27,000 patients showed that the surveyed patients who started pregabalin therapy for neuropathic pain or psychiatric illnesses have substantially reduced their intake of benzodiazepines after 6 months, in some cases up to 48% [90]. The results were similar in another study in Spain where pregabalin was used for the discontinuation of benzodiazepine usage and helped the subjects in significantly reducing their anxiety symptoms [81]. We also know, however, that pregabalin has an abusive potential. It has been reported to increase the effect of heroin and its effects on respiratory depression, especially when combined with opiates and benzodiazepine can lead to overdose [89]. It is unclear in our case whether the patients were using pregabalin for a particular clinical indication or for abusive purposes. 10% of patients in one ORT program in Germany were found to be using pregabalin without any clinical indications [89]. From our experience, it is still relatively easy in Germany to obtain a prescription from neurologists as it is still widely used as an off-label medication for the indications listed above.

4.5 Chronic pain

Treating chronic pain in drug addicted patients continues to pose great challenges among health care providers. During the period of the study at WPS, we often came across patients who were recently discharged from the hospital expressing their concerns of being stigmatized, their ORT at times altered or discontinued and most frequently about the under-treatment of their pain. In most cases it was due to the medical staffs being reluctant to provide adequate analgesia and were rather suspicious of their reported level of pain. This frequently led to early inpatient discharges and an overall general negative perception and distrust in the medical system. The inadequate control of acute pain has been suggested to lead to decreased responsiveness to opioid analgesics [91] and can subsequently lead to the development of chronic pain.

We have also on the other hand, experienced first-hand the challenges of prescribing analgesia to ORT patients or patients with a history of substance abuse in the hospital, especially in the emergency room. This was in most part due to the lack of understanding of ORT, their interactions with a wide range of psycho-active substance the patients might be taking, the fear of overdose, the fear of iatrogenically provoking a relapse, and given the patients' often long and complex history of drug abuse, the clinicians' mistrust in the patients reported severity of pain. This resulted to the inadequate administration of analgesia in acute settings, whereas in most cases ORT patients are more pain sensitive compared to opiate naive patients and require a much higher dose of opiates due to their increased level of tolerance. In addition, ORT patients are likely to suffer from opiate-induced hyperanalgesia as a consequence of the extended period of ORT and opiate agonists, and this results in the neuro-plastic changes in pain activity leading to increased pain sensitivity [91].

According to a study by Jamieson et.al conducted with 248 ORT patients across three centers in the U.S in 2000, more than 60% of their patients were found to suffer from chronic pain, and this has shown significant correlations to psychiatric disturbances, more prescription and non-prescription medication use and greater belief that they were under-treated [92]. In comparison, only 28% of patients from both practices in our study reported to have suffered from chronic pain. This comprised of roughly equal percentages of total female and male patients. As illustrated in table 3.4 and figure 3.9, we have found that patients with chronic pain not only have significantly higher BDI-II scores compared to those without pain, they also consume the highest amount of benzodiazepine usage of 190mg in diazepam per week compared to the other co-morbidities studied. Furthermore, 66% of benzodiazepine used by chronic pain patients were obtained illegally. BDI-II scores are strongly correlated to a positive diagnosis of depression and anxiety with a significance of 0.01. From this we can deduce that higher consumptions of benzodiazepine in patients with chronic pain are possibly due to its positive correlation with depression and anxiety. Moreover, due to the possible effect of opiate-induced hyperalgesia, the use of benzodiazepines helps ORT patients to achieve adequate pain relief where they otherwise cannot from the use of opiates and over-the-counter analgesics alone.

In this study, no significance between chronic pain and high severity of insomnia were

found, though all patients suffered insomnia to some degree. Patients with chronic pain in other studies have, however, reported significant sleep disturbances and that poor sleep quality can be attributed to higher pain intensities and vice versa. Poor sleep quality can originate from the use of opiates as discussed in the previous section.

Thus, the management of pain in ORT patients can be difficult even for the most experienced physicians. Firstly, patients should always be reassured in acute settings that their pain will be treated seriously and aggressively and that their usual dosage of ORT will be continued. This decreases patients' anxiety and fear for in-patient admissions and allows the basis to build a trusting relationship with their treating physicians. ORT patients have a higher hypersensitivity to pain, higher percentages of those being females [93]. It has been recommended to administer high dose of short-acting opiates at frequent intervals for pain relief. Opiates should also be given on a regular basis to avoid intervals of pain and anxiety between doses. The use of mixed opiate agonists and antagonists, such as Targin have also been discouraged due to the risk of withdrawal symptoms [91]. Multimodal analgesia such as NSAIDS, COX-2 inhibitors and acetaminophen, as well as the use of certain anticonvulsants and antidepressants might also be administered in conjunction with opiates to decrease opiate needs.

Benzodiazepines do have a profound effect on relieving muscle spasms especially in patients with back pain, and many physicians in Germany prescribe long-acting benzodiazepines such as lorazepam during acute phases of pain for up to 6 weeks. The issue arises when patients are "lost" in the process due to inadequate follow-ups to initiate the weaning process to prevent excessive usage and addiction. This also leads to "doctor shopping" when a centralised system for monitoring prescription of addictive medications are not yet available in Germany, making it almost impossible for doctors to track the actual dosage of medications patients are using. Current strategies in managing chronic pain include strict regular reviews of the use of all pain medications making sure that the medications are appropriately prescribed in the indicated dosages and any issues with medication side effects should be promptly addressed. Volkow et. al also suggested urine drug testing before every prescription is written, to assess for the presence of other opioids or drugs of abuse [62]. In this thesis, we have identified the close connection between depression and chronic pain. Therefore, it is important to regularly assess patients' mood using scales such as BDI-II, also as another method of assessing the effectivity of the treatment of chronic pain. Aside from pharmacological therapy, the management of chronic pain should also involve adjunctive therapies such as cognitive behavioural therapy, physiotherapy, and in certain cases acupuncture, nerve stimulation and epidural injections [62]. As mentioned previously, slowly decreasing the dose of opiate in cases of opiate-induced hyperalgesia might help with pain relief [62]. This is however difficult to achieve in clinical practice, given the diagnosis of hyperalgesia is entirely based on clinical suspicions and tapering the dose of opiates in patients with chronic addiction can lead to withdrawal symptoms rather than improvements in pain. If the clinician decides to taper the dose of opiates given to the ORT patients, it is important that the treatment process is explained to and initiated together with the patients so that the opiate dose can be gradually tapered in a controlled manner. Physicians can also try switching to another class of opiates, which has been

shown to be effective in some cases [62]. Lastly, effective management of sleep disturbance can also improve symptoms of hyperalgesia, making it important to continuous monitor the PSQ scores during ORT therapy.

4.6 Limitations to the study

4.6.1 Design of the study

The primary limitation to this study is that it is a cross- sectional study. As mentioned previously, the data are collected in a cross- sectional study at a single point in time to examine the relationship between the disease, in our case, being insomnia and depression and other variables of interest, being different ORTs, benzodiazepine abuse, chronic pain and unemployment. This gives us merely a snapshot of the frequency of disease at a point in time, but it has limited usage in drawing valid conclusions about any possible causality because the risk factors and outcomes are measured simultaneously. It has the advantage that multiple variables and outcomes can be measured at the same time and it is easy and cost-effective to gather the data. This is different to a longitudinal study, where patients are being followed over an extended period of time to better explore the relationship between the disease and the variables.

The structure of a cross-sectional study poses several disadvantages in the accuracy in analyzing the objectives of our study. First of all, PSQ and BDI-II scores should be recorded before commencing ORT and then in preferably 3-monthly intervals to see if ORT had a true impact on the scores. The impacts that a particular ORT had on the BDI-II or the PSQ scores in this study were basely on the patients' self- reports at a single point in time. Similarly, the effect of psychotherapies and antidepressants on the BDI scores should be evaluated over a period of treatment, so should the usage of benzodiazepines on patients with anxiety, depression and insomnia after appropriate therapies. Moreover, BDI-II and PSQ scores are strongly affected by many reversible social factors, such as unemployment and a break in the relationship, therefore, the scores are heavily situational dependent and analyzing them at a single point in time cannot give us a satisfactory answer to the root causes of the problems.

4.6.2 Study size

To obtain accurate results the study should contain large enough data points to ensure that they are not by bias nor by chance. In our study, we have found from the results of some of the calculations that there were tentative relationships between certain variables but no statistical significance and this was suspected to be due to the small patient size of the study. One such example is the tentative negative correlation between diamorphine and insomnia, but with only 14 patients on diamorphine therapy no statistical relationship was found. This study only involved a total of 113 patients from only two Opiate- Substitution practices in Munich. In general, patients at NBC also tend to have more comorbidities, are

more therapy resistant, are at risk of severe complications, thus, they are being treated at a university hospital facility instead of in a practice. To be able to use our results on a broader scale and be able to compare within the general population, data would need to be collected from different outpatient facilities, and from different German states. Future studies should preferably involve other facilities offering diamorphine therapy.

4.6.3 Data collection methods

Since the data on exposures and outcomes were collected simultaneously, we set the specific inclusion and exclusion criterion at beginning of the study to ensure data from those patients who are at risk for the studied outcomes are identified. But as this study was entirely voluntary, many patients who fitted the inclusion criterion did not participate. The quality of the data collection was also dependent on the questionnaires, the interviewers, and the availability of access to patients' medical records. In this case, only myself and a medical student were involved in conducting the study. I was responsible for surveying the patients in WSP and the other was solely at NBC. The patients were strictly supervised during the study to the best of our efforts but due to various factors, some patients did not fully complete the study and others took several attempts over days to finish the questionnaire. Some questions on the survey had been also altered or re-worded several times throughout the study period to make them more understandable to some patients. The results have therefore been subjected to both responder and interview biases.

We found the non-response in the questionnaires was a particular problem when we calculated the results as it could have resulted in a large bias when measuring the outcome. The reasons for not answering a question also differed from patient to patient. For example, they might have been hesitant to admit to their current illicit drug usage amounts, the source of their benzodiazepine usage and in other cases, they did not recall the name of the antidepressants they were currently using. Furthermore, as with all questionnaires-based studies, one of the main limitations to the study is that many of the questions are subjective, so we more or less solely rely on what the patients tell us. One of the examples is the wide range reported in the quantities of the illicit drugs consumed particularly impacts on the statistic results of the study.

4.6.4 Patient medical records

Throughout the study we have had access to the patients' medical files from both clinics and this aided us greatly in obtaining the patients' past medical history, hospital admission records, past psychotherapies, current medication lists, as well as results of random drug screens. We have found however, from both practices that the indication, source and the intended duration of prescribed benzodiazepines to ORT patients to be sub-optimally documented in the records. This has made it difficult to track the origin and the actual amount of their current legal benzodiazepine usage. The records often showed a significant different amount to what the patients actually claim to be taking but this was mostly outdated. Most patients as shown in the results use a combination of prescribed and illegal

sources of benzodiazepines. It would be easier to plan methods of its usage reduction if the reasons behind its legal prescription were known for each patient.

4.6.5 BDI-II Inventory

We used BDI-II inventory to assess current moods in the patients. This was however, in retrospect not ideal for our patient group because many co-morbidities such as, chronic pain and substance abuse can cause a falsely high score due to symptom overlap. For future studies, we should be considering using the BDI Fast Screening for ORT patients instead. Firstly, BDI Fast screen consist of 7 instead of 21 questions as in BDI-II inventory, which makes the survey easier to understand for patients with substance abuse disorder. It has also been constructed to reduce the number of false positives in patients suffering from both somatic and substance disorders [72].

4.7 Recommendations for future research projects

One of the main strengths of a cross-sectional study is that it is good for providing a quick overview of the prevalence of health issues in a specific population and assessing its burden of disease. This is helpful in generating future hypotheses and further interesting research projects. Following on from this study there are several areas of interest that could are worthwhile to further investigate.

First of all, although we were able to produce a good overview of the prevalence and burden of depression and insomnia among ORT patients, we were unable to assess the effect of different variables, such as the type of ORT, benzodiazepine usage, unemployment etc. on the severity of depression and insomnia over an extended period of time. Furthermore, many of the variables in our original hypothesis, for example, co-morbidities which could be related to sleep dysfunction such as COPD, restless leg syndrome and peripheral neuropathy have not yield statistical significance to PSQ scores in our study, possibly due to the small number of participants. An interesting project would be conducting similar studies in many ORT centres of different scales across Germany, where the BDI-II and PSQ scores of patients, as well as their social situation, usage of illicit drugs, and psychiatric and somatic co-morbidities are assessed on a 3 to 6 monthly basis. From this we can assess if the results we have observed in this study between the variables are also held true on a larger scale.

Another interesting topic is to investigate the source of prescribed benzodiazepine in ORT patients. So far, we have found that patients continued to use benzodiazepines past the intended duration and many have been suspected to have ‘doctor shopped’ from varies practices after the scripts were used up. This could lead to several interesting potential projects. Firstly, one project could investigate the pattern of prescription by physicians, this being the intended duration of benzodiazepine usage for various indications, the types and dosages, the frequency of subsequent follow-ups and if measures to reduce its usage has implemented. The quality of physicians’ documentations and assessments should also

be evaluated, especially to look at if the re-assessment of the indication of benzodiazepine usage has taken place and whether alternate therapies were offered. This would partly prevent unnecessary prolonged usage of benzodiazepines leading to addiction.

A project following this would be to follow the usage of benzodiazepines in conjunction with non-pharmacological therapies for insomnia, such as cognitive behavioural therapy, to assess the effectivity of these therapy methods and if they would lead eventually to a decrease in benzodiazepine consumption and an improvement in PSQ scores over time. Similarly, we can investigate the effectivity of different antidepressant therapies in reducing benzodiazepine usage in the treatment of ORT patients with depression and anxiety. In this study, we have found a negative correlation between the use of antidepressants and benzodiazepines in affected subjects. It would be interesting to assess this correlation on a larger scale longitudinal study to see not only the effect that antidepressants have on the BDI scores in ORT patients, but also to follow the dose of benzodiazepines these patients use over the period of antidepressant therapy. Likewise, the effect of non-pharmacological interventions for depression can be assessed with or without concurrent use of antidepressants on BDI scores and benzodiazepine usage.

Furthermore, as mentioned previously, the use of benzodiazepines has been shown to increase with the length of ORT. Given the above, effective treatment of opiate addiction, psychiatric illnesses and insomnia should have proposed the opposite. With the emergence of new benzodiazepines in some countries such as phenazepam and etizolam in Scotland, this had led to a rise in drug related deaths [25]. Thus, it is even more essential to follow-up the benzodiazepine usages of patients from the time they enter ORT to prevent further abuse.

Given the high surge of benzodiazepine usage in recent years, another project would be to build a computer system for physicians to check for such 'doctor shoppers'. Physicians should be able to access when, where and the dosage of the last drug prescription and patients who obtain prescriptions simultaneously from multiple physicians should be flagged in the system. As mentioned in the introduction section of the thesis, such systems are already in place in Australia and parts of the United States.

Another interesting area of research would be to further investigate chronic pain syndrome in ORT patients. As demonstrated in the results section, poorly managed chronic pain is strongly associated with depression, and in other studies ORT patients have exhibit symptoms of opiate- induced hyperanalgesia, which makes providing adequate analgesia to ORT patients a challenge for physicians. The fear of being undertreated for the pain has also caused delayed hospital presentations for wounds and injuries, leading to long-term health complications. Since chronic pain in ORT patients was not the main topic of this thesis, we did not ask patients about the types of prescription and non/prescription medications they used for pain relief, check if their opioid addictions are related to their chronic pain, and if they feel that they are being undertreated in for their pain. One possible study would be to examine the questions above, ask the patients to fill out a pain score questionnaire and compare the pain scores over duration of the ORT therapy to see if there is evidence of opiate- induced hyperanalgesia.

Finally, although hepatitis C was not a main topic in this thesis, I found it particu-

larly interesting that so many patients from both practices were not treated despite the high tolerance and effectivity of the new antiviral therapy. Current guidelines recommend that active injection drug use should not exclude patients from HCV treatment, and no significant interactions were reported between DAA and opiate substitution regimes [94]. Thus, making the ORT patients suitable candidates for the current therapy. One suggested project would be following ORT patients with positive diagnosis of hepatitis C up with 6 monthly assessments of abdominal ultrasound, baseline blood results, documentations of follow-up visits to the Hepatologists and if they have not been treated, exploring reasons for the lack of treatment.

Kapitel 5

Conclusions

We as clinicians have known for many years now that ORT patients are a high-risk group of patients who are battling with not only ongoing drug addictions, but are also suffering from complex somatic and psychiatric disorders. The severity of their treatment has been compounded with their lack of insight into their illnesses, incompliance and inadequate social support. Having worked as the primary care physician of 120 ORT patients at WSP during the course of this study in 2015, we have experienced first-hand the impacts of drug addiction. Moreover, the challenge of providing a satisfactory level of care to these patients and to witness an adequate change in their physio-psycho-social status was much greater than we had previously anticipated.

This study has demonstrated the importance of BDI-II questionnaires as quick and effective screening tools to identify and monitor the progress of depression in ORT patients. The modified Fast BDI questionnaire in our opinion, can be used as a quick and simple method for general psychiatric evaluation by primary physicians who have not had extensive training in psychiatry. It should be used and documented routinely as a part of general assessment of every patient before commencing ORT and as a continuous assessment throughout the course of substitution therapy to identify and treat those who are at risk of depression.

We have furthermore identified and demonstrated the extensive use of benzodiazepines in ORT patients, both through illegal abuse and clinical prescriptions. A key driver of benzodiazepine prescription has been for insomnia. Hence, clinicians need to take essential steps to reduce unnecessary and excessive benzodiazepine prescribing for sleep disturbance, but rather search and treat its underlying cause. The primary treatment of insomnia should be based on non-pharmacological approaches to improve sleep hygiene and treating organic causes, and to identify and discontinue medications that may be causing sleep dysfunction. Thus, a continuous evaluation of sleep function using the PSQ questionnaire is a good way to monitor the patients' progress and response to therapies for insomnia throughout the course of substitution therapy. More importantly, the higher scores in PSQ is an additional way to identify those who might potentially be at risk for benzodiazepine abuse.

Through the use of both questionnaires routinely completed throughout the course of ORT, we do not only improve patients' psychiatric health and functional status, but also

reduce the use of benzodiazepines and illicit drugs, which consequently decreases opiate related deaths.

We have also shown that ORT patients are more prone to higher levels and longer durations of pain and they are more likely to self -manage and suffer from depressive symptoms rather than seeking help. ORT patients also from experience tend to be far more often undertreated for their pain in the hospital compared to other patients. To understand and better manage the complexity of concurrent pain and multi- drug dependency among patients on ORT, we need to first and foremost earn the trust of these patients. Establishing a solid doctor-patient concordance is quintessential in achieving good quality of clinical outcomes. These patients are particularly vulnerable to distrusting the health care system and therefore, the trust that their care provider will care for their interest is the foundation for effective clinical outcomes. We need to be regularly assessing these patients' pain scales, especially those who are being treated for their acute pains; identify and treat the underlying cause of pain; educate and provide alternative analgesic approaches to prevent self- medication.

Lastly, we have established in this study the influence of some social factors in depression and sleep quality. With regular involvement of social workers on a demand basis in both clinics in the study, we can improve their overall quality of life by aiding patients with finding jobs and suitable accommodation. However, with high unemployment rate among these patients shown in this study we should ask ourselves the question if the current intervention strategies can be improved.

Overall, this is a much needed but small- scale study of a vulnerable patient group within a very much underrecognized and understudied area of medicine. Throughout the course of this study, we have found that there is in general a lack of literature in treating issues in and surrounding opiate substitution not only in Germany, but also world-wide especially in developing countries. Although this study has only scratched the surface of a small multitude of challenges facing us currently in two opiate substitution clinics in Munich, we believe it will have clinical implications not only for the caregivers working in these clinics, but also for psychiatrist, social workers and general practitioners involved in the treatment of patients battling opiate addiction. Together with the development of the new Hepatitis C therapy, our new understanding of chronic pain treatments, the introduction of buvidal and the expanding availability of diamorphine therapy in Germany, findings in this study will hopefully help to point to areas of future research and improvement of clinical practices. One day from all of which we can use to improve the overall quality of life of opiate addicted patients.

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